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DISEASES OF CHILDREN

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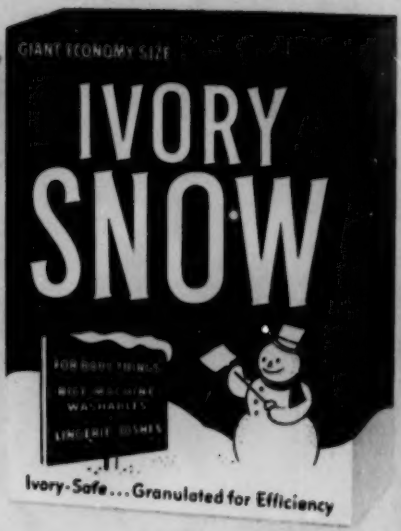

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DISEASES OF CHILDREN

Study of the Role of Antigen Dosage in the Treatment of Pollenosis and Pollen Asthma

DOUGLAS E. JOHNSTONE, M.D., Rochester, N. Y.

Because of the relative frequency of pollenosis ("hay fever") in childhood and the tendency for it to be followed by asthma or perennial allergic rhinitis, a critical re-evaluation of the treatment of this condition seems indicated.

The purpose of this study was to determine by means of a controlled study the relative value of the three most widely used techniques of hyposensitization therapy.

Methods

The protocol for the study was written before the experiment was begun. Population sampling and random selection procedures were previously discussed with a statistician. It was decided that the experimental population be made up entirely of children referred to the pediatric allergy clinic of the Strong Memorial Hospital. The only weed pollen extract to be used was ragweed.

As each new patient with a history of pollenosis was referred to the pediatric allergy clinic, he was assigned by strictly random selection procedures to one of the following groups: 1. Highest tolerated dose. Treatment in this group was begun with a relatively small dose of ragweed pollen, averaging 0.10 ml. of a 1:50,000 dilution of ragweed in Coca's solution. This was equivalent to 10 Noon units of ragweed extract. The dose was gradually increased at weekly intervals until an average dose of 0.50 ml. of between 1:200 and 1:500 dilution (1250-2500 Noon units) was reached. If a child exhibited any signs of a constitutional reaction or had a large local reaction at the site of injection, the dose was arbitrarily reduced by 0.15 ml. of whatever dilution he was getting at the time. This proved necessary in only one child. In all groups, once the "top dose" was reached that dose was given unchanged at four-week intervals by the perennial method and continued at weekly intervals during the ragweed season. After the season ended, the four-week interval was resumed until the following ragweed season, and so on. 2. The 1:5000 group. This group was likewise begun on relatively small doses of ragweed pollen extract, and the dose was increased weekly until an arbitrary "top dose" of 0.50 ml. of a 1:5000 dilution (100 Noon units) was reached. This dose was then continued at the same intervals as in Group 1. This method of treatment has been advocated by Ratner.[1] 3. The 1:10,000,000 group. Treatment of this group was begun with a dose of 0.10 ml. of a 1:10,000,000 dilution of ragweed extract. The dose was increased weekly up to an arbitrary "top dose" of 0.50 ml. of this same dilution (0.50 Noon unit), and this dose was then maintained at the same intervals as in the other groups. This method of treatment has been advocated by followers of French Hansel.[2] 4. Controls. This group received weekly injections of buffered saline, labeled "pollen mixture, 1:20,000." A dosage schedule similar to that of Group 3 was set up. The true identity of this mixture was known only to me.

The procedure for studying each child was as follows: Every patient was first seen in the general pediatric clinic, where a medical history and physical examination, followed by routine urine analysis, complete blood count, tuberculin test, and, in some instances, chest x-rays were completed. A complete allergy history was then obtained.

Submitted for publication Jan. 2, 1957; accepted March 4, 1957.

From the Department of Pediatrics and the Department of Radiation Biology, The University of Rochester School of Medicine and Dentistry and the Strong Memorial Hospital.

TABLE 1.—*Relative Air Ragweed Counts in Rochester, N. Y., in 1955 and 1956*

Year	Number of Days During Ragweed Pollenation Season When Pollen Count Exceeded		
	100 Granules/ Cu. Yard of Air	200 Granules/ Cu. Yard of Air	300 Granules/ Cu. Yard of Air
1955	27	14	12
1956	12	1	0

and, if warranted, skin testing with routine pollens, molds, epidermoids, and foods was performed. The scratch method of testing[8] was used first. All inhalant allergens which failed to cause a positive scratch reaction were rechecked with intradermal testing.[8] The history and skin test findings were checked by an allergist other than myself. At that point I assigned each new child to one of the above-mentioned four groups by random selection. Upon completion of the allergic study each mother was told which allergens had given significant reactions. She was also advised on avoidance or minimizing of exposure to inhalant allergens, especially pollens. In addition, each mother was instructed in the use of symptomatic medications for pollenosis and asthma.

To help in the evaluation of these children during the ragweed season a questionnaire was prepared for use of the physicians giving the injections. It sought information regarding the amount of symptomatic medication used, relative severity of the various "hay fever" symptoms, and the mother's over-all evaluation of the child's pollen-induced symptoms in comparison with previous ragweed pollen seasons. If a mother or a physician suspected asthma, the child was examined by a staff physician or a pediatric allergist other than myself. All children in this study were observed during at least two separate ragweed seasons, and most were seen during three seasons.

Because the ragweed pollen count in Rochester varies from year to year, it was decided to evaluate each group at the end of the pollen season of 1956. Table 1 compares the relative amounts of air-borne ragweed pollen in Rochester, N. Y., during the ragweed pollenating seasons of 1955 and 1956. This Table shows that there was much less ragweed pollen in the air in this area in 1956 than in 1955. However, it was felt that, if this fact tended to minimize symptoms in treated groups, it also meant that any increase in symptoms in the control group compared with the treated groups would be all the more significant. Of 175 children who were initially placed in one of the four groups, adequate follow-up information has been obtained for 112 children. The data on these form the basis of this report.

TABLE 2.—*Degree of Relief of Hay Fever Symptoms in the Four Groups Studied as Indicated by Mothers' Responses to Questionnaires*

Group *	Total No. in Group	No. of Patients Who Were Said After Treatment to Be		
		Same	Worse	Better
Highest tolerated dose (1:200-1:500)	29	14	1	14
1:5,000	26	16	1	9
1:10,000,000	31	16	7	8
Controls	26	13	7	6

* The dilution designated in each group represents the highest concentration of ragweed pollen extract used in treatment.

Results

Table 2 summarizes the subjective evaluation by the patient's mother of the relative severity of hay fever symptoms in comparison with pretreatment pollen seasons. These data were not subjected to statistical analysis because of their subjective nature.

Table 3 summarizes the incidence of pollen asthma in the four groups of children known to be clinically sensitive to ragweed pollen, before and after treatment. Before these data were analyzed statistically, they were rearranged as shown in Table 4. This Table is designed to demonstrate the influence of the various types of treatment on the prevention or amelioration of pollen asthma in the ragweed-sensitive child. It shows that, in the children receiving the

TABLE 3.—*Incidence of Pollen Asthma in the Four Experimental Groups Before and After Treatment*

Group *	Total No. in Group	Children with Pollen Asthma				Children with Hay Fever but No Asthma			
		Before Treatment		After Treatment		Before Treatment		After Treatment	
		No.	%	No.	%	No.	%	No.	%
Highest tolerated dose (1:200-1:500)	29	22	76	7	24	7	24	22	76
1:5,000	26	15	58	7	27	11	42	19	73
1:10,000,000	31	21	68	23	74	10	32	8	26
Controls	26	14	54	18	69	12	46	8	31
Totals	112	72	64.3	55	49.1	40	35.7	57	50.9

* The dilution designated in each group represents the highest concentration of ragweed pollen extract used in treatment.

TABLE 4.—*The Influence of Type of Treatment on the Prevention or Amelioration of Pollen Asthma*

Group (Total)	Children with Pollen Asthma Before Treatment					Children with Pollenosis Without Pollen Asthma Before Treatment				
	Total No.	Lost Asthma on Treatment		Asthma Persisted in Spite of Treatment		Total No.	No Pollen Asthma After Treatment		Developed Pollen Asthma in Spite of Treatment	
		No.	%	No.	%		No.	%	No.	%
Highest tolerated dose (1:200–1:500) (29)	22	15	68	7	32	7	7	100	0	0
1:5,000 (26)	15	9	60	6	40	11	11	100	0	0
1:10,000,000 (31)	21	4	19	17	81	10	4	40	6	60
Controls (26)	14	1	7	13	93	12	7	58	5	42
Totals (112)	72	29	40	43	60	40	29	73	11	27

"highest tolerated pollen dose," 68% who had pollen asthma before starting therapy lost their asthma. None of them who had previously had hay fever without asthma developed pollen asthma after treatment was begun. The results in the group labeled "1:5000" were nearly as good.

In the group labeled "1:10,000,000," only 19% of the children who had pollen asthma before treatment lost their asthma after treatment. On the other hand, 60% of this group developed pollen asthma for the first time on treatment. Among the control group only 7% who had had previous pollen asthma lost their asthma as an apparent result of treatment, and 42% developed asthma for the first time in spite of treatment.

Table 5 summarizes the results of testing the statistical significance of the differences between each of the three treated groups and the control group, and each other group. It may be noted that the groups labeled "highest tolerated dose" and "1:5000" fared better in this respect than either of the other two groups.

Comment

Rockwell [5] was among the first to advise "that the maximum tolerated dose is the one which gives the best results and in general the higher the dose, the better will be the clinical results." This has been the guiding principle of the "highest tolerated dose" method, used in this clinic for years. Until now, however, this concept has been taught without benefit of a controlled clinical study.

In evaluation of our study it must be kept in mind that the treatment of pollenosis or pollen asthma may depend to some extent on

TABLE 5.—*Analyses of Differences in Amelioration or Prevention of Pollen Asthma Among the Four Groups Studied*

Contrasting Groups	Children With Pollen Asthma Before Starting Treatment			Children With Hay Fever Without Pollen Asthma Before Starting Treatment		
	χ-Square *	P *	Significant Difference	χ-Square	P *	Significant Difference
Controls vs. highest tolerated dose	20.58	<0.001	Yes	22.64	<0.001	Yes
Controls vs. 1:5,000	8.77	<0.001	Yes	6.80	<0.01	Yes
Controls vs. 1:10,000,000	3.27	<0.10	No	0.40	0.80	No
1:10,000,000 vs. highest tolerated dose	13.75	<0.001	Yes	5.75	<0.02	Yes
1:10,000,000 vs. 1:5,000	3.48	<0.05	?-No	13.17	<0.001	Yes
Highest tolerated dose vs. 1:5,000	7.10	<0.01	Yes	Uncomputable	....	No
All four groups together	21.33	0.001	Yes	13.09	0.001	Yes

* P represents the probability of the results (and χ-square) being as discrepant as those observed when there is actually no difference in the population proportions compared. When P is smaller than 0.05, we reject the hypothesis or idea that the population proportion in the groups compared is the same.

the locality. Levin [6] stated that "undoubtedly those who treat hay fever on the eastern seaboard can achieve good results with smaller doses due to the lower pollen count generally prevalent in that area as compared to the midwest where the pollen count is very often extremely high."

Ratner's recommendation [1] of not exceeding a dose of 0.30 ml. of a 1:5000 dilution of ragweed extract apparently was based on his belief that a larger dose was unnecessary. He felt that the anamnestic response or booster effect of this moderate-sized dose would be sufficient to produce just as good clinical results as higher doses, which he felt might result in generalized anaphylactic reactions. The present study would seem not to bear out his basic assumption, although children in this study treated by his method did remarkably better than either the controls or those treated by the Hansel method. On the other hand, Ratner's warning of possible generalized reactions from excessively high doses of ragweed pollen is well taken. In Levine's report,[6] for instance, it was noted that constitutional reactions to injections occurred in children in his clinic at the rate of 1 in 2000 injections, with use of approximately 10 times the maximum concentration used in this clinic. Levin recommends a maximum dose of 15,000 to 30,000 Noon units, compared with our top dose of 2500 units. Our reaction rate during the period of this study was 1 generalized reaction in 3900 injections.

It is possible that more favorable results might have been achieved in the two groups called "highest tolerated dose" and "1:5000" had the hyposensitization material also included pollens of other weeds as well as extracts of the several mold spores known to be capable of producing rhinitis or asthma during the ragweed season in this area. However, these were deliberately omitted in an effort to simplify the experimental conditions.

One might further consider the psychological effect of the injection itself, since 7% of the control group lost their asthma, according to their mothers, "thanks to these injections."

As might be expected, the efforts to gain objective data on the effect of hyposensitization therapy on hay fever proved impractical. This is to be expected, since the nature of and the variety of data needed to make such an objective evaluation would require more objectivity and training than most parents have. Furthermore, the mothers of many clinic patients often color their information about their child's progress either so as to make things appear better than they are (in order to "please" the clinic physician) or so as to deliberately give the impression that their child is doing worse than he actually is (in order to give vent to some sense of disapproval of the doctor or the clinic routine generally). Nevertheless, the subjective data obtained from these interviews with the mothers closely paralleled the more objective data on results of treatment on amelioration or prevention of pollen asthma.

It should be noted that the relatively high incidence of pollen asthma in each of the groups studied certainly exceeds that likely to be found in the general pediatric population. This stems from the fact that only those children in our clinic population who failed to respond to symptomatic therapy or who seemed particularly ill found their way to our specialized clinic.

Summary and Conclusions

In a controlled study of the effect of hyposensitization on ragweed sensitivity, the role of antigen dosage was evaluated by placing children on one of three different treatment regimens or in a control group. Of children receiving the "highest tolerated dose," 68% who had pollen asthma before starting therapy lost it. None who had hay fever without asthma before treatment developed pollen asthma after treatment was begun. Children receiving an intermediate maximum dosage of 0.50 ml. of a 1:5000 dilution of ragweed pollen extract did almost as well. The control group and the fourth

group, who received exceedingly minute doses of pollen extract, did significantly less well, as evidenced by failure of amelioration or prevention of pollen asthma after "treatment" in a year when ragweed pollenation was remarkably scant.

The house staff physicians of the pediatric department helped in this study. Dr. Marilyn Smelzer supervised the house staff physicians and served as a "qualified but disinterested" expert. Dr. Arthur Dutton, of the statistics section of the department of radiation biology, analyzed the data. Dr. Lee Crump, chief statistician of the department of radiation biology, gave valuable advice in the initial planning of the study. Dr. Jerome Glaser provided the data on the ragweed pollen counts in 1955 and 1956.

P. O. Box 287, Station 3 (20).

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Plasma Inorganic Phosphate and Glucose of Prepubertal Children Taking Testosterone

HANS G. KEITEL, M.D., Philadelphia
With the Technical Assistance of J. Blakely

It has been known for many years that the inorganic phosphate concentration of plasma is elevated in early life.[1-5] The high values found during the newborn period may result from a relatively high phosphorus intake, temporary neonatal hypoparathyroidism, low glomerular filtration rate, or a failure of the renal tubule to respond to parathyroid hormone.[1-5] After the first year of life, however, the elevation has been attributed by many to the presence of a high concentration of growth hormone.[6-9]

Hamilton, Bunch, Mestler, and Imagawa recently reported that after orchiectomy the plasma inorganic phosphate of young adults rose to the prepubertal level within one to three weeks.[10] They interpreted their data, and those from the literature, as indicating that sex hormones exert a depressant effect on the plasma phosphate concentration and concluded that sex hormones, rather than a decreasing concentration of growth hormones, may depress the phosphate concentration during puberty. However, not all data reviewed by Hamilton et al. were in agreement with this hypothesis.[10] It was decided to investigate the effect of testosterone medication on the plasma phosphate concentration in dwarfed prepubertal children to see whether a reduction regularly occurs.

Methods and Material

The subjects, nine prepubertal children between the ages 6 and 11 years, were more than two standard deviations under the height found in normal children of comparable age.[11] With the exception of one patient with gonadal dysgenesis and another with Addison's disease, the dwarfism was not known to be associated with an endocrine disturbance. In three instances the patients were also somewhat underweight for their size, indicating the possibility of "nutritional dwarfism." In three cases a genetic component to the dwarfism was considered likely.

The patients received 25 mg. of methyltestosterone orally three to four times a day, one dose being given on arising, another at bedtime, and the other one or two during the day. Usually a two-week supply was given to the mother. The timing of the requests for additional medication indicated that the testosterone was administered regularly. Diet was not controlled. In all instances the appetite increased markedly, and the body weight increased from 6% to 15% in one month. Except for hoarseness in one patient, no undesirable clinical side-effects were noted. Blood samples were taken at 9 to 10 a. m. with the patient fasting.

Materials.—Phosphate was measured by the method of Fiske and Subbarow, with an analytical accuracy of ±4%.[12] Glucose was measured by the method of Nelson-Somogyi, with an analytic accuracy of ±4%.[13]

Results

The Table and Figure 1 present the plasma phosphate concentration of nine prepubertal children before, during, and after the administration of 16 courses of methyltestosterone. The 20 pretreatment values were in the range previously described by Danowski in normal children between the ages of 5 and 10 years.[14] Fifty-six determinations were obtained during testosterone administration; the majority of these were in the range of normal young adults.[15] Plasma phosphate values in the adult range were seen as early as the fourth day of

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Plasma Inorganic Phosphate in Nine Children Given Methyltestosterone

Case	Course of Testosterone	Before Testosterone * Plasma Inorganic Phosphate		Testosterone Period †						Off Testosterone †			
1	1	5.3	4.8	3 4.4			15 4.1			1 4.9		35 5.0	
2	2	5.1		3 5.0	5 4.7	7 4.6	10 4.7	14 4.2	21 3.9	5 4.9		28 5.6	
	3	5.4		2 4.6		12 4.7	20 4.4	24 4.1	39 3.2	10 3.6	27 4.5	86 5.3	150 4.6
3	4	4.0		4 3.2		11 3.4		18 3.4		23 4.0			
	5	4.2			10 3.2		22 3.2			15 3.2	33 3.9	93 4.7	
4	6	4.9		3 4.4	6 4.1	10 4.0	30 4.5			7 4.3			
	7	4.6			9 3.8					7 4.4	14 4.8		
	8	4.7	5.0	17 3.9		25 4.3				32 5.0			
5	9	4.6		5 3.5	9 3.4	15 4.1	20 3.8			21 5.6			
	10	4.9		13 4.3		26 4.3				30 5.3			
6	11	4.5		3 4.7	6 4.0	10 4.1	14 4.6			9 4.9			
	12	5.4	5.2	7 4.8		20 5.0		39 4.5		9 4.3	26 4.6	100 5.1	
7	13	4.2		4 3.0	7 3.5	11 3.7				20 4.4			
8	14	4.9		3 4.2	4 4.2	7 4.0	11 3.3	18 3.9		21 5.2		142 4.6	
9	15	4.6		3 3.9	4 3.6	7 4.3	9 3.7	11 4.4	18 3.7	13 4.5			
	16	5.0	5.8	3 4.6	12 4.4	21 4.0	35 3.8			16 4.0	35 4.3	44 5.2	141 4.6

* Milligrams per 100 ml.; determinations made two weeks to three months apart.
† Top number, days of testosterone administration; bottom number, plasma inorganic phosphate, milligrams per 100 ml.

testosterone administration. There was a tendency for the subjects with the lower values to have them during testosterone administration. The probability that the observed reduction in the plasma phosphate was due to chance was less than 1 out of 20 in each of seven time periods of four days each during testosterone administration. After testosterone was discontinued the phosphate concentration rapidly returned to the pretreatment values in most instances (Table).

The plasma concentration of glucose of eight children—four studied on two occasions—before, during, and after the administration of methyltestosterone is shown in Figure 2. There was a fall to an abnormally low level of the glucose concentration during the first 10 to 15 days in three subjects on five occasions.* In one patient a value of 150 mg. per 100 cc. was noted on the third treatment day. The average post-testosterone glucose values are similar to those found in the control period.

Comment

The present data indicate that a large dose of methyltestosterone exerts an immediate depressant effect on the plasma phosphate concentration of prepubertal children. On the basis of these data one cannot con-

* Morning hunger was a prominent symptom in most patients receiving testosterone, but dizziness, sweating, and syncope were not reported.

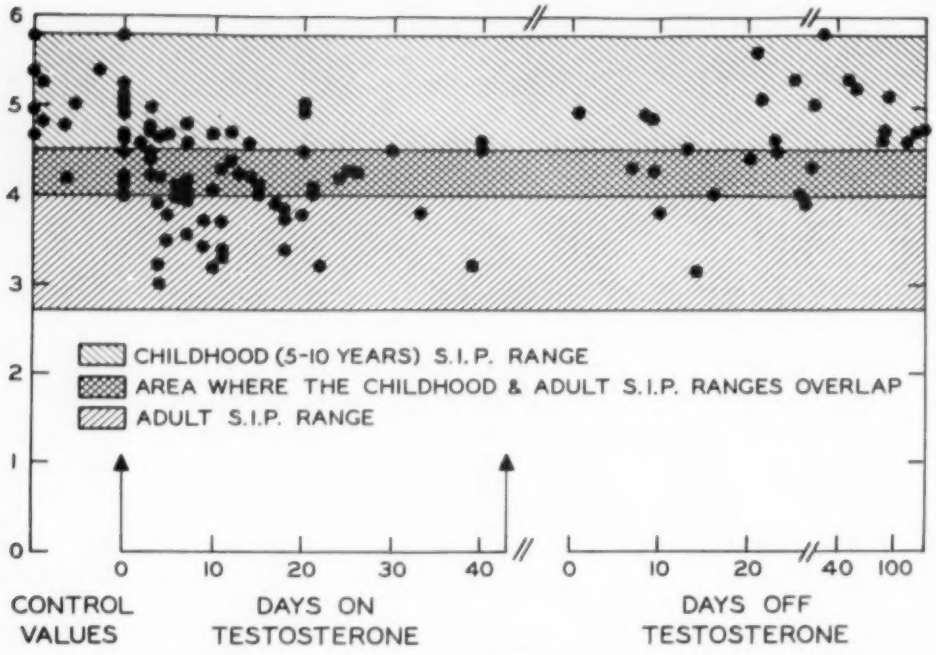

Fig. 1.—The plasma phosphate concentration (milligrams per 100 cc.) (ordinate) before, during, and following the administration of methyltestosterone (abscissa). Values between 4 and 6 mg. per 100 cc., corresponding to those usually seen in prepubertal children, were found during the control period, and values from 3 to 4.5 mg. per 100 cc., corresponding to those usually seen in adults, were found during the period of testosterone administration.[16]

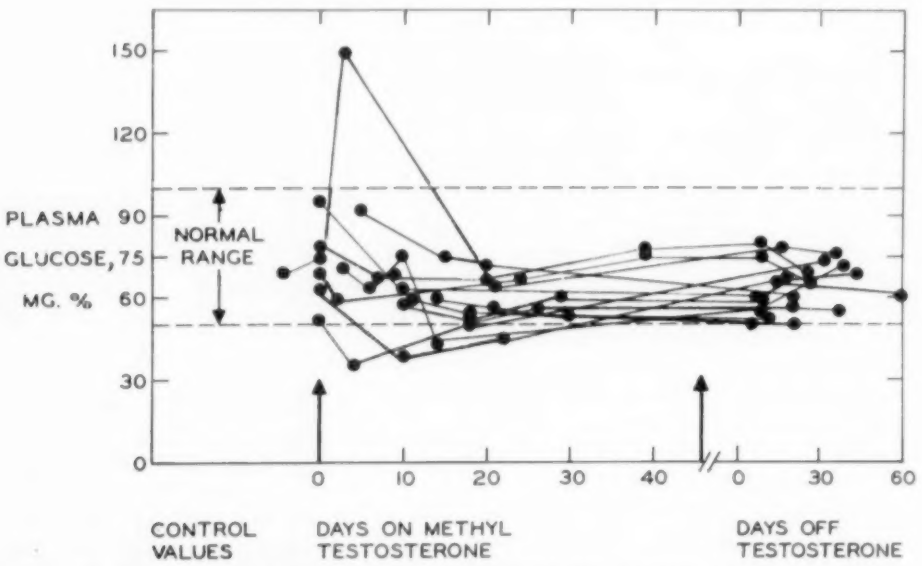

Fig. 2.—The plasma glucose concentration (ordinate) before, during, and following the administration of methyltestosterone to six prepubertal children.

clude that the decrease in the plasma phosphate which develops in males during puberty is due to the presence of testosterone, for the amount of testosterone used in the present study exceeds the amount formed endogenously. The observed drop may therefore represent a "pharmacologic" rather than a "physiologic" effect. Against the former possibility is the observation that the phosphate values fell only to the range usually found in postpubertal subjects.[14]

The increased intake of food which was reported to have occurred in the patients would have resulted in a sufficiently increased intake of phosphorus to have compensated for the small increased retention of phosphorus known to occur during the administration of androgens[15]; therefore the decrease in the fasting phosphate concentration probably was not due to phosphorus deficiency.

A "renotropic" effect of testosterone was suggested in some of the patients, since the urea clearance rose during testosterone, on the average 30%.[16] However, as the fraction of the filtered phosphorus reabsorbed by the tubules largely determines the amount of phosphorus which appears in the urine, a change in the glomerular filtration rate probably is less important in determining the fasting phosphorus concentration than is the renal tubular-parathyroid hormone status.[17]

The reduction of the plasma glucose concentration in some cases during testosterone medication indicates that a change in carbo-

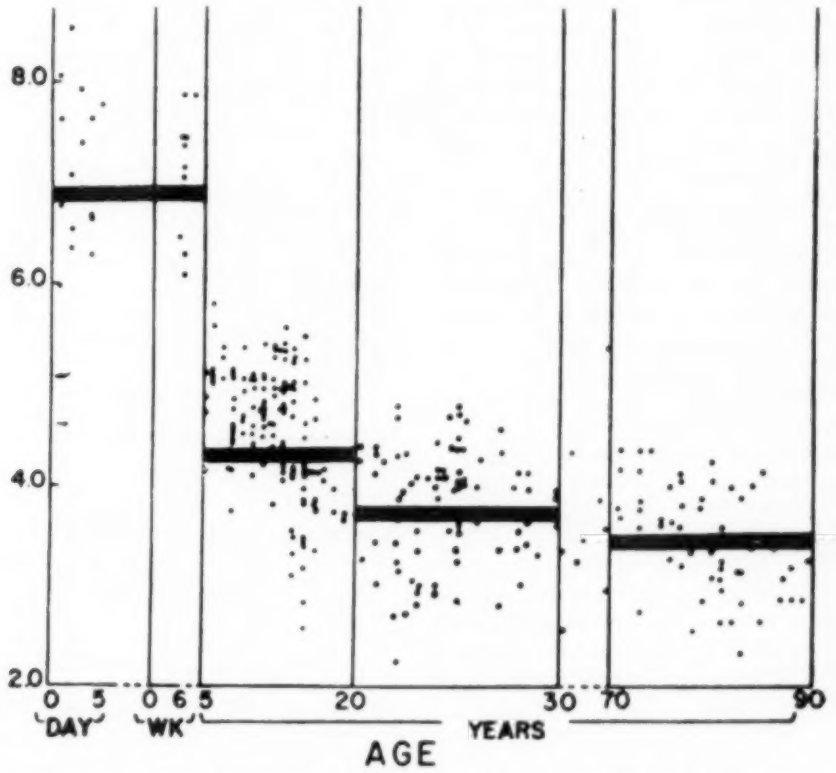

Fig. 3.—The phosphate concentration of serum from birth until 90 years of age. During puberty (approximately age 10 to 14 years) both prepubertal and adult values are found. (Reproduced with permission from Elkington, J. R. and Danowski, T. S.: Body Fluids, Baltimore, Williams & Wilkins Company.)

hydrate metabolism may be related to the phosphorus findings, for a reduction in the blood phosphate frequently occurs in association with a fall of the blood sugar following insulin administration and following glucose loading.[18-20] Against this possibility are the absence of a reduction in the plasma glucose concentration in some of the patients and the absence of a reduction in the potassium concentration in any of the patients [21]; the concentration of potassium as well as phosphate is usually reduced following an acute reduction in the blood sugar concentration by glucose loading and insulin administration.[22,23]

A relationship of the phosphorus changes to the plasma calcium concentration can be discounted, since in several of the present subjects no significant change in the plasma calcium concentration was observed during the administration of methyltestosterone.[21] The adult subjects of Hamilton et al., in whom castration was followed by an elevation of the plasma phosphorus concentration, also did not have a change in the serum calcium concentration.[10]

The plasma phosphorus concentration of normal children of varying ages, as reported by Danowski, can be interpreted as supporting the hypothesis that the sex hormones are related to the fall in the plasma phosphate which occurs at puberty.[14] Danowski's data indicate that the fall occurs from about the 9th to the 13th year of life (Fig. 3), during which time sexual development usually becomes manifest. The indirect evidence for the case that sex steroids exert a depressant effect on the plasma phosphate concentration during puberty therefore appears to be more impressive than the indirect evidence for the case that a change in the metabolism of growth hormone results in such a change, especially in view of the fact that rapid growth occurs during this period.

Summary

A decrease in the fasting plasma inorganic phosphate concentration was seen in nine prepubertal children given 16 courses of methyltestosterone in doses of 75 to 100 mg. per day. A decrease in the plasma glucose concentration was seen in some subjects. The findings are discussed in relation to the hypothesis that sex hormones are related to the decrease in the plasma phosphate concentration which occurs at puberty.

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Skin Eruptions in Children Due to Probenecid

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This report presents a rather unusual observation of skin eruptions in children treated with the renal tubule physiologic blocking agent probenecid (*p*-[dipropylsulfamyl]benzoic acid). This drug has the ability, when administered with penicillin, to produce a twofold to tenfold increase in the blood penicillin level. For this reason, it seemed to us that the drug might be an ideal agent for the treatment of β-hemolytic streptococcal infections and other infections amenable to penicillin therapy. We attempted to assay its value in these infections in children. This report will be limited, however, to a discussion of the skin eruptions observed. Our observations suggest that these apparently nonserious reactions are related to the duration of treatment and to individual idiosyncrasy rather than to the dosage on an age or weight basis.

Method

Our studies were made during the school year 1955-1956. We used two different combinations of penicillin and probenecid; a tablet containing 250,000 units of potassium penicillin G plus 0.25 gm. of probenecid (Remanden 250) and a liquid preparation, of which each teaspoonful (4.9 ml.) contained a suspension of the same amount of penicillin but twice as much probenecid (0.50 gm.). During the major part of the period of observation, 1 tablet was given three times a day for a period of 10 days or 1 teaspoonful of the suspension was given twice daily for the same period. Thus, in a period of 10 days, the child received a total dose of 7,500,000 units of penicillin and 7.5 gm. of probenecid, when given the tablets, or 5,000,000 units of penicillin and 10 gm. of probenecid, from the suspension. No attempt was made to change the dosage on a weight or age basis. Consequently, there was considerable variation in the amount of probenecid per pound of body weight.

Later in the course of the study, in an attempt to reduce the frequency with which the drug eruptions occurred, the total dose was maintained at essentially the same level, but the duration of treatment was reduced to seven days. In this schedule, 1 tablet was given four times daily for one week (total dose 7,000,000 units of penicillin plus 7 gm. of probenecid) or 1 teaspoonful of the suspension was given three times daily for the same length of time (total dose 5,250,000 units of penicillin and 10.5 gm. of probenecid). Almost all patients were seen after therapy, and, if a drug eruption occurred, they were usually observed at that time or shortly thereafter. In all cases included in this study, the mother was questioned as to how well the drug was taken and in what amount. She was also queried about the occurrence of rash. It was thus possible to arrive at a reasonably accurate estimate of incidence of appearance of the rash in relation to the age of the child, the amount of drug taken, and the duration of therapy.

A total of 232 patients received these combinations of penicillin and probenecid. Of these, the data on 202 who took the medication adequately were complete enough to be included in the study.

Results

The first skin eruption was observed in a 3-year-old girl (Case 5) who was being treated for a Group A Type 28 β-hemolytic streptococcal infection with 1 Remanden tablet three times daily. On the ninth day of medication she developed a fever (temperature 102 F) for which no explanation could be found. On the following day the fever disappeared and she developed a maculopapular eruption which suggested roseola, rubella, or a sulfonamide eruption. By the next day, it was apparent that the eruption was neither roseola or rubella. It covered the child, including the palms of the hands and soles of the feet. On the face it had become confluent and intensely red. Despite her startling appearance, she did not appear ill, pruritus was not pronounced, and the white blood cell count was essentially normal. In the course of the next two to three days, the rash gradually subsided, but brownish staining, somewhat similar to that occurring after rubeola, lasted for several weeks.

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TABLE 1.—*Summary of Patients Developing Skin Eruptions While Receiving Probenecid*

Case	Sex	Age, Yr.	Wt., Lb.	Diagnosis *	Form of Med.†	Drug, Gm. Given by Mouth	Time of Rash	Fever	Duration of Rash, Days	WBC, Thousands	% Polymorphonuclear Cells	Remarks
1	F	1	20	S.T.	Susp.	1.5	8	0	1	..	..	
2	M	1	25	S.T.	Susp.	3.5	8	0	3	9.4	50	
3	F	2	33	S.T.	Susp.	7.5	9	0	3	..	..	
4	M	3	30	C.A.	Tab.	6.5	9	0	2	8.8	45	
5	F	3	33	S.T.	Tab.	?	10	Yes	5	6.8	32	Temp. 102 F
6	F	3	36	S.T.	Susp.	7.0	9	0	14	11.4	..	Had chickenpox simultaneously
7	M	4	40	S.T.	Tab.	6.2	9	Yes	?	10.3	..	Itching; temp. 102 F
8	M	4	44	O.M.	Susp.	10.5	8	0	7	..	..	7-day schedule
9	M	5	38	S.T.	Tab.	?	?	0	?	..	..	
10	F	5	40	S.T.	Tab.	5.5	9	0	1	8.4	48	
11	F	6	40	Car.	Tab.	5.5	8	0	?	6.9	40	
12	F	6	42	O.M.	Tab.	7.0	8	0	2	18.4	48	7-day schedule
13	M	6	45	S.T.	Tab.	5.5	8	0	1	10.1	50	
14	F	6	45	S.T.	Susp.	7.5	9	0	3	6.2		
15	M	6	47	S.T.	Tab.	6.5	10	0	2	..	..	
16	M	7	45	S.T.	Tab.	7.0	10	0	2	11.2	..	
17	M	7	47	S.T.	Susp.	8.5	10	0	1	..	..	
18	F	7	48	S.T.	Tab.	6.5	9	0	3	..	..	Upper thighs only
19	M	7	52	S.T.	Susp.	7.0	8	0	5	6.8	32	Some hives also
20	M	7	54	S.F.	Tab.	6.0	8	0	3	9.4	50	Finished all pills; rash no worse; some itching
21	F	7	60	S.T.	Tab.	7.0	8	Yes	1	8.8 7.4 10.2		Temp. 101 F; 7-day schedule
22	F	7	60	S.T.	Susp.	?	?					
23‡	M	8	50	S.T.	Susp.	8.0	9	0	1½	..	..	Mother reported "covered from head to foot"
24	M	8	60	S.T.	Tab.	6.2	9	0	6	6.7 11.8	28 60	3d day rash 5th day rash
25	F	8	70	S.T.	Susp.	7.5	9	0	10	12.2	58	Cheeks fiery red; slightly red
26	F	9	60	S.T.	Tab.	7.0	9	0	..	6.2		
27	F	9	69	Car.	Tab.	7.5	?10	0	2	..	..	
28	F	9	72	S.T.	Susp.	7.5	9	0	..	..	..	
29	M	10	62	S.T.	Tab.	5.2	9	0	?	..	..	
30	F	11	97	S.T.	Susp.	9.0	14	0	2	5.7	68	Missed some med; mother gave some to make up
31	M	14	72	S.T.	Susp.	7.5	9	0	2	6.2	50	

* S.T., Streptococcus sore throat; C.A., cervical adenitis; O.M., Otitis media; Car., Streptococcus carrier.
† Tab., tablets (250,000 units penicillin G+0.25 gm. probenecid); Susp., suspension (250,000 units penicillin G+0.5 gm. probenecid per teaspoonful).

Subsequent to this case, 30 other children developed skin eruptions (Table 1). Although a few were equally intense, most were lighter in color, of shorter duration, and not associated with fever, malaise, or other symptoms. A typical eruption of moderate severity is depicted in Figures 1 and 2. Although itching did occur, it was not common or pronounced. With remarkable regularity, the patients developed the rash while in the ninth calendar day of taking the drug. White blood cell counts were essentially normal, and the polymorphonuclear cells were generally not suppressed. No evidence of hemorrhagic tendency was noted, although one child with a very intense rash had the same type of small mild superficial hemorrhage of the skin as is sometimes seen after the rash with rubeola. Platelets appeared normal in number in a few cases when stained blood smears were examined.

While these rashes were appearing in the group treated with probenecid and penicillin, at least twice as many children were receiving penicillin alone, both orally and intramuscularly, and none showed any similar rash. Occasional urticarial eruptions did occur in these others. As a matter of fact, in addition to the 31 eruptions reported here, there were three urticarial rashes in this series receiving probenecid. We felt, however, that these were due to the penicillin, since they occurred within the first few days after administration of the drug and since penicillin alone had previously caused similar eruptions in two of the children.

In those who took the probenecid in approximately equal amounts there was no significant difference in the reaction rate according to age (Table 2). Nor were we able to demonstrate any difference on a basis of weight (Table 3). Actually, in both these tables the reaction rate appears, if anything,

Fig. 1.—Typical probenecid rash on buttock and leg.

Fig. 2.—Typical probenecid rash on face and chest.

TABLE 2.—*Incidence of Probenecid Skin Reactions in Relation to Age and Dosage* *

Age, Yr.	Total Dosage of Drug, Gm.						Total Cases		
	5.1–7.5			7.6–10.5					
	Cases, No.	Cases with Rash		Cases, No.	Cases with Rash		No.	No. with Rash	% with Rash
		No.	%		No.	%			
1–3	2	2	100.0	32	4	12.5	34	6	17.6
4–6	44	7	15.9	34	2	5.9	78	9	11.5
7–9	37	9	24.3	29	4	13.8	66	13	19.7
10 and over	12	2	16.7	12	1	8.3	24	3	12.5
Total	95	20	21.0	107	11	10.3	202	31	15.3

* Variation in dosage was due to the amount of drug given daily and duration of treatment.

TABLE 3.—*Incidence of Probenecid Skin Reaction in Relation to Weight and Dosage* *

Weight, Lb.	Total Dose of Drug, Gm.						Total Cases		
	5.1–7.5			7.6–10.5					
	Cases, No.	Cases with Rash		Cases, No.	Cases with Rash		No.	No. with Rash	% with Rash
		No.	%		No.	%			
15–29	1	0	0	11	2	18.2	12	2	16.7
30–44	23	7	30.4	38	3	7.9	61	10	16.4
45–59	37	6	16.2	26	3	11.5	63	9	14.3
60 or more	34	7	20.6	31	3	9.7	65	10	15.4
Unknown	0	0		1	0	0	1	0	0
Total	95	20	21.0	107	11	10.3	202	31	15.3

* Variation in dosage was due to both daily dose and duration of treatment.

TABLE 4.—*Incidence of Probenecid Skin Reactions in Relation to the Duration of Medication*

Duration of Treatment, Days	Total Dosage Approximately Equal: Total Cases, No.	Reactions, No.	Reactions, %±S.D.
7	49	3	6.1±3.4
10	153	28	18.3±3.1
	202	31	15.3

higher in those that took the lower dosage! However, when essentially the same amount of drug was given over a 7-day period rather than for the 10-day period, the reaction rate was significantly lower (Table 4) (probability due to chance less than 1 in 100). In fact, by the ninth day, when the rashes usually appeared, those children on the 7-day schedule had taken more probenecid than had those on the 10-day schedule.

Comment

From these observations it would appear that there was no evidence to indicate that the amount of probenecid on a weight or age basis was related to the incidence of skin eruptions. On the other hand, there was evidence that the incidence of skin reactions was related to the time interval over which the drug was taken. That the skin eruptions described here were due to probenecid seems beyond question. They had none of the characteristics of penicillin reactions and did not appear in any of a much larger series of penicillin-treated patients in the same population at the same time. To us they were indistinguishable in appearance from the morbilliform skin eruptions often caused by sulfonamide medication, and since probenecid is chemically related to this group of drugs this is not surprising. That they were occasionally very pronounced and associated with fever (two of our cases) also seems clear. However, none of the reactions observed appeared dangerous. There was no evidence of agranulocytosis, nor were there any urinary changes. In fact, a number of the patients, despite the rash, took the drug for several more days according to schedule without any apparent harmful effect. Although we did not feel justified in continuing the drug beyond 10 days or in giving it again once a reaction appeared, this would probably be a relatively safe procedure, if one may judge by analogy to the sulfonamides.

The almost predictable regularity with which the rash appeared after eight days of taking the medication, regardless of the relation of dose to age or weight, and the decrease in incidence occasioned by reducing the length of time the medication was taken reminds one of a serum-sickness-like reaction. Although the data are not included in our report, we have frequently given probenecid for periods of less than a week and have never observed a skin eruption under these conditions.

Boger and Strickland,[1] in a report of the use of probenecid in 2502 patients, mention 34 cases (1.35%) of skin rash. They described the rashes reported as scarlatinaform, diffuse maculopapular, urticarial, or merely "allergic" and as usually accompanied by fever. Since their report is a compilation of cases from many sources, the details are lacking. In at least five of their cases, penicillin was also used, which they felt might be the actual cause of some of the skin eruptions.

The difference in the incidence which they report (1.35%) and ours (15.3%) may be due in part to the fact that our cases were children who were very closely observed by the parents, who had been instructed to report the appearance of any rash to us. Approximately 1400 of their cases were given the drug for from "1 to 14 days," but, from the report, it is not clear how many had the drug for less than seven days. The dosage which they recommend is approximately 2 gm. daily for adults. This is in fair agreement with the smaller doses we used in children (0.75 to 1.5 gm. daily). However, in their series they reported eight "unmistakable cases of hypersensitivity" but no fatalities.

It is not our purpose here to review the literature dealing with the side-reactions of probenecid but merely to report our experi-

ence with what appeared to be a fairly common benign group of skin eruptions. We also wish to point out the interesting relation of the incidence of these skin rashes to the duration of medication.

Conclusions

In 202 children given a combination of penicillin and probenecid, 31 maculopapular eruptions occurred, which appeared to be benign in character. The incidence of these rashes seemed to be related to the duration of therapy rather than to the amount of probenecid given.

This study was supported in part by Sharp & Dohme, who also supplied the penicillin and probenecid mixtures used. Dr. Lee Crump gave advice on the statistical methods used. Mrs. Clinton Wolcott, Miss Noreen Ireland, Miss Ann Ruby, Miss Barbara Stevens, and Mrs. Kathryn Donahue helped in this study.

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Spontaneous Fractures in Tuberculous Meningitis

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Spontaneous fractures of the sternum have been described in adult patients with tuberculosis.[1] No evidence of intrinsic bone disease has been found and no disturbance of calcium or phosphorus metabolism was noted in these cases.

Furthermore, the apparent high incidence of rib fractures in tuberculous patients[2] raises the question of an effect of the infection on bony structures.

However, up to now patients with tuberculosis are not considered particularly liable to decalcification, except insofar as unusually prolonged bed rest may lead to demineralization.

The scope of this paper is to report on four patients, all of them infants, who during their treatment for tuberculous meningitis developed spontaneous fractures of the lower extremities without any evidence of localized tuberculous lesions on the areas of the fractures.

We do not consider the factor of bed rest alone as constituting a satisfactory explanation for these fractures.

Report of Cases

CASE 1.—A 12-month-old boy was admitted to the hospital in 1948 with the clinical picture of severe meningitis.

The father was suffering from pulmonary tuberculosis. On admission the tuberculin reaction was strongly positive and the cerebrospinal fluid showed 1.5 gm. of protein and 30 mg. of sugar per 100 ml. and 170 cells, mostly lymphocytes.

X-rays of the chest revealed tuberculous adenitis, and funduscopic examination showed a moderate papilledema. The patient was treated intensively with streptomycin intramuscularly and intrathecally, and therapeutic progress was satisfactory.

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Four months after admission a painful swelling on the left knee was noted. An x-ray revealed a linear fracture of the medial condyle of the left femur. Twenty-four days later a roentgenogram showed a satisfactory callus formation around the fracture.

CASE 2.—A 14-month-old girl was admitted to the hospital in 1948 with a history of pyrexia and vomiting of 25 day's duration.

Tuberculin reaction was strongly positive.

X-rays of the chest showed tuberculous adenitis, and a spinal tap revealed a protein content of 0.90 gm. per 100 cc.; sugar, 30 mg. per 100 cc., and 540 cells, predominantly lymphocytes.

The patient was intensively treated intramuscularly and intrathecally with streptomycin and made a rapid recovery. He was fairly active in bed and his appetite and weight gain were satisfactory.

Two and a half months after admission a flaccid paralysis of the right lower extremity was noted.

An x-ray revealed a greenstick supracondylar fracture of the right femur which on subsequent x-rays showed an excessive callus formation the size of which was almost double the size of the femur.

CASE 3.—A 12-month-old boy was admitted to the hospital in 1955 with a history of pyrexia and vomiting of 15 day's duration. Tuberculin reaction was positive.

Rigidity of the neck was noted, and a spinal tap revealed 1.5 gm. per 100 cc. protein, 0.15 mg. per 100 cc. sugar, and 128 cells, mostly lymphocytes.

The patient was intensively treated with streptomycin, isoniazid, and cortisone intramuscularly and intrathecally and made a satisfactory recovery.

Five and a half months after admission bilateral painful swelling of both lower extremities was noted. X-rays of the spinal column and long bones revealed an extensive osteoporosis and an extreme thinning of the periosteum, while those of the lower extremities showed a bilateral Y-shaped fracture of the femoral condyles with some impaction. A month later, after removal of the plaster, the bony union was solid.

Laboratory evaluation revealed the following: Ca 10.1 mg. per 100 cc.; P, 4.8 mg. per 100 cc.;

alkaline phosphatase, 12.2 Bodansky units; potassium, sodium, and chloride, normal; total protein, 5.8 gm. per 100 cc. A Sulkowitch test in the urine was 1+, and a paper chromatographic study for urinary amino acids was within normal limits.

Seven months after admission and a month and a half after the last fractures, bilateral swelling of the left tibia was noted. X-rays of both lower extremities revealed a greenstick fracture of the upper third of the left tibia which healed easily with a plaster splint.

CASE 4.—A 12-month-old girl was admitted to the hospital in 1956 with a history of anorexia, restlessness, and, subsequently, semicomatose condition of eight days duration.

The patient on admission was in a comatose state and convulsing. A spinal tap revealed 1 gm. per 100 cc. protein, 0.20 mg. per 100 cc. sugar, and 90 cells, predominantly lymphocytes. On the basis of clinical and laboratory criteria her tuberculous meningitis was considered as severe. X-rays of the chest revealed miliary tuberculosis. There was splenomegaly and hepatomegaly.

The patient was intensively treated with streptomycin, isoniazid, and cortisone intramuscularly and intrathecally. The course of the disease was quite stormy, complicated two months after admission by viral hepatitis. The child kept convulsing occasionally, and she remained permanently spastic.

Three months after admission after mild physical therapeutic manipulations pathological fractures of both lower extremities were verified roentgenologically.

X-rays revealed an epiphysiolysis of the right distal epiphysis of the femur and a supracondylar fracture of the left femur. Both fractures healed with superfluous callus formation after a month's immobilization.

Ca and P determinations were within normal limits. A urinary Sulkowitch test was negative.

Comment

Although few reports describing spontaneous fractures in adult tuberculosis exist in the literature, nevertheless none of them incriminates the infection as the cause of the effect on bony structures. It is a well known fact that prolonged bed rest leads to extensive demineralization.

The four described patients raise a number of interesting questions, in view of the fact that their immobilization was incomplete and their protein intake good.

As they all belong to the infantile age group their motor accomplishments under normal conditions are restricted to walking if led, standing, exploiting toys, etc. All of our patients, with the exception of one (No. 4), after an average of thirty days of treatment were sitting in bed able to control a fairly normal infantile motor behavior and were eating fairly well. Therefore, since immobilization was not complete, it seems rather improbable that prolonged bed rest would account for the described spontaneous fractures.

Two of our patients (No. 3 and No. 4) were given cortisone intramuscularly and intrathecally in addition to standard methods of therapy. Since spontaneous fractures under cortisone therapy have been already described in the literature,[3] it seems probable that prolonged steroid therapy enhances osteoporosis and increases the possibility of spontaneous or pathological fractures.

Durand reported on 24 patients with tuberculous meningitis out of which 16 presented osteoporosis, occasionally extensive, while in a control group of 15 patients with nonmeningeal tuberculosis, only one displayed diffuse osteoporosis.[4] Phosphorus in these patients was low and calcium was normal.

According to this author osteoporosis in these cases was due to an involvement of the diencephalon.

We consider probable in the four described cases that a similar mechanism is involved which could be explained either by a toxic action of streptomycin on the hypothalamus or by an involvement of the diencephalon in the meningitic process.

Possibly of a similar nature are hypertrichosis and obesity, occasionally encountered and described in the treatment of tuberculous meningitis.[5]

Summary

Four patients with tuberculous meningitis belonging to the infantile age group presented spontaneous fractures in the course of their hospitalization.

We do not consider bed rest alone as sufficient evidence to explain these fractures.

It is postulated that in the course of tuberculous meningitis the hypothalamus is involved either by a toxic action of streptomycin or by an involvement of the diencephalon in the meningitic process.

Since cortisone enhances osteoporosis, extreme caution should be exercised when administering steroids in a long-range treatment.

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The Electrocardiogram in Ventricular Septal Defect

A Correlative Study of Fifty Cases

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The electrocardiogram in ventricular septal defect has received relatively little attention, and standard works on congenital heart disease and cardiology have referred to it as either being normal or presenting no striking abnormality.[1-4] More recently the occurrence of left ventricular hypertrophy, combined hypertrophy, complete right bundle branch block, and incomplete right bundle branch block have been variously commented upon.[5-7] In view of the variety of combinations of shunt volume and right ventricular pressure found in patients with ventricular septal defect, it should not be surprising if a variety of electrocardiographic patterns are encountered.

A study of the electrocardiograms of 50 patients with ventricular septal defect upon whom cardiac catheterization had been performed has led us to conclude that the electrocardiogram reflects with reasonable accuracy the type and magnitude of hemodynamic abnormality present.

Material and Methods

At least one standard 12-lead electrocardiogram was obtained in each case, and in a few of the cases vectorcardiograms were obtained. Each of the patients had undergone cardiac catheterization and a diagnosis had been established by this as well as the usual clinical methods. The cases were obtained from consecutive catheterizations carried out during the past three years.

The patients ranged in age from 4 months to 45 years, with 33 of the patients being 10 years of age or younger. Cases were excluded in which there were associated cardiac malformations, but cases are included in which there was marked pulmonary hypertension and varying degrees of right-to-left shunt.

The electrocardiographic criteria of ventricular hypertrophy which were used are similar to those compiled by Kossman.[8] Concentric right ventricular hypertrophy was usually manifested by a shift in the mean spatial QRS axis to the right and anteriorly and by the presence in lead V_1 of a taller than normal R wave showing an Rs, R with or without slurred or notched upstroke, or a qR together with some delay in the intrinsicoid deflection. The incomplete right bundle branch block pattern of an RSR′ in lead V_1 with normal or slightly prolonged QRS duration was considered in a separate category, since it may be a manifestation of mild right ventricular hypertrophy, a conduction disturbance, or a normal variant due to a slight positional change of a normal QRS vector loop.

Large diphasic QRS complexes in two or more of the precordial leads and occasionally in the standard leads are probably a manifestation of combined right and left ventricular hypertrophy and are considered in a separate category in this study.[9]

The electrocardiographic diagnosis of left ventricular hypertrophy was based on the usual criteria. The pattern of a left precordial qRs with large Q and delayed intrinsicoid deflection associated with varying degrees of right ventricular hypertrophy was regarded as a manifestation of left ventricular hypertrophy. The pattern of diastolic overloading of the left ventricle consisted essentially of the usual criteria of left ventricular hypertrophy in association with tall upright concordant T waves over the left precordium.[10]

Results

Figure 1 graphically summarizes the electrocardiographic findings and their relation to the major hemodynamic alterations determined by cardiac catheterization. In this series only two of the patients presented normal electrocardiograms. Concentric right

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From the Departments of Medicine of the Bishop Clarkson Memorial Hospital and the University of Nebraska College of Medicine.

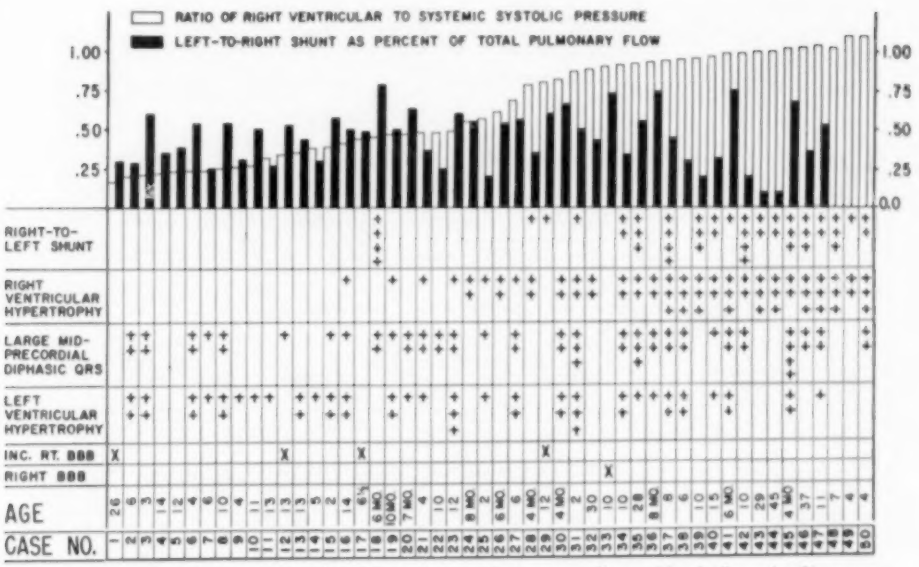

Fig. 1.—Summary of the physiologic data and electrocardiographic findings in 50 cases of ventricular septal defect.

ventricular hypertrophy with or without other electrocardiographic abnormalities was noted in 29 cases. There was a high degree of correlation between the ratios of right ventricular to systemic systolic pressure and the presence of right ventricular hypertrophy by the electrocardiogram. None of the patients with pressure ratios of less than 0.41 showed this pattern.

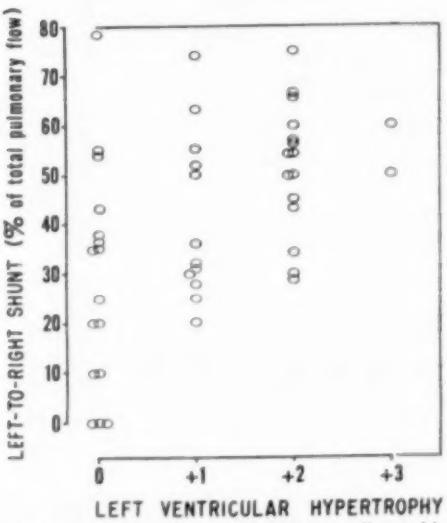

Fig. 2.—The relation of electrocardiographic left ventricular hypertrophy to the volume of left-to-right shunt.

The electrocardiographic diagnosis of left ventricular hypertrophy with or without associated abnormalities was made in 29 of the patients, and there was a moderate degree of correlation between the volume of left-to-right shunt and the presence of left ventricular hypertrophy ($r=0.61$; $p=<0.01$) when the 5 patients with complete or incomplete right bundle branch block are excluded. Figure 2 shows the relation of the electrocardiographic evidence of left ventricular hypertrophy to the volume of left-to-right shunt. No patient with a left-to-right shunt volume of less than 20% of the total pulmonary flow showed left ventricular hypertrophy. Of 23 patients showing left-to-right shunt volumes of less than 40% of the total pulmonary flow, 10 showed left ventricular hypertrophy by the electrocardiogram. Of 27 patients having left-to-right shunt volumes of 40% or more of the total pulmonary flow, 19 showed electrocardiographic left ventricular hypertrophy. The electrocardiographic pattern of diastolic

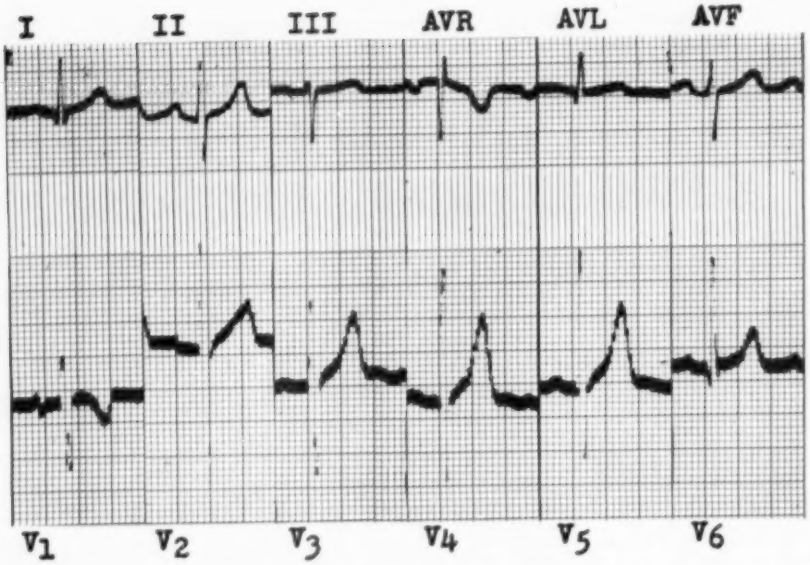

Fig. 3 (Case 9).—A 4-year-old boy with a small left-to-right shunt and normal right ventricular pressure. The electrocardiogram shows Grade I left ventricular hypertrophy as manifested predominately by left-axis deviation.

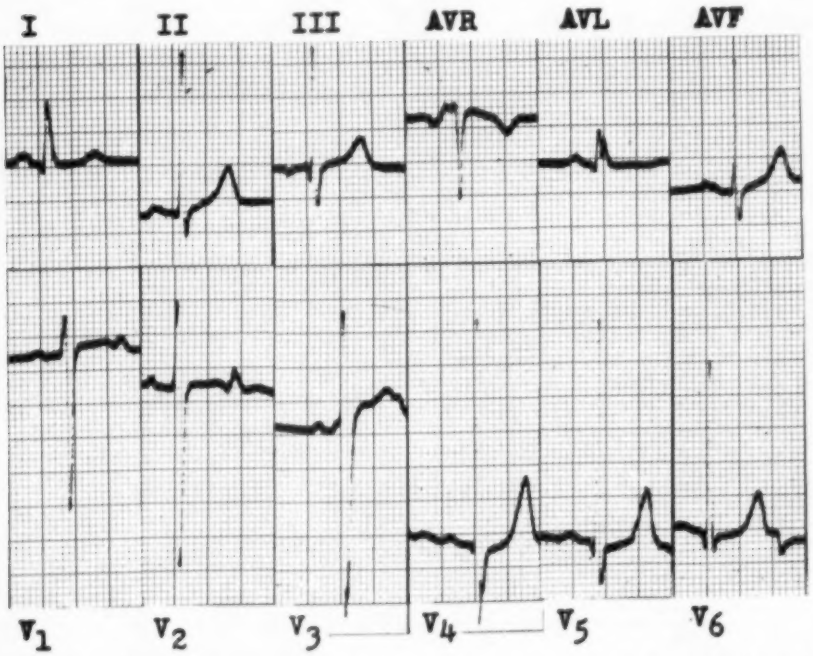

Fig. 4 (Case 10).—An 11-year-old boy with a moderately large left-to-right shunt and normal right ventricular pressure. The electrocardiogram shows Grade I left ventricular hypertrophy primarily manifested by the tall R waves and delay of the intrinsicoid deflection in V_5, V_6.

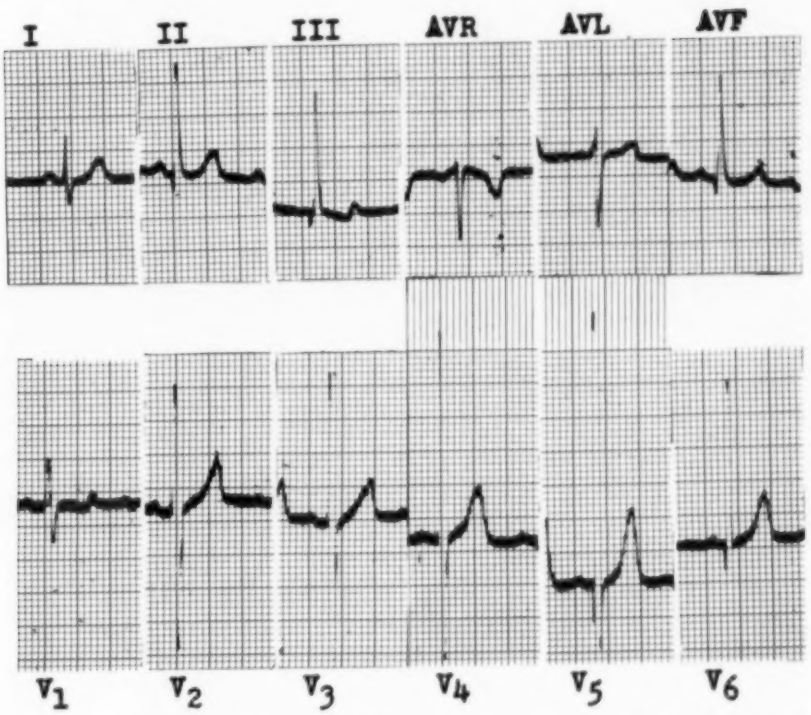

Fig. 5 (Case 16).—A 16-year-old girl with a moderately large left-to-right shunt and slight right ventricular hypertension. The electrocardiogram shows Grade I right ventricular hypertrophy manifested primarily by the increased R/S ratio in V_1. There is Grade I increase of the voltage of the diphasic QRS in V_2, V_4. There is Grade II left ventricular hypertrophy shown by the deep Q and tall R in V_5, V_6.

overloading of the left ventricle was present in seven of the patients and was usually associated with moderate left-to-right shunt and little or no pulmonary hypertension. The prediction of the volume of left-to-right shunt from the electrocardiogram was much less reliable than the prediction of the right ventricular pressure from the electrocardiogram.

The finding of diphasic QRS complexes of large voltage in the mid-precordial leads seemed to be distributed somewhat randomly throughout the series, although there was some tendency for this finding to be most prevalent when a significant left-to-right shunt existed in the presence of some pulmonary hypertension, and it was most frequently found in the presence of electrocardiographic evidence of both right and left ventricular hypertrophy. Thirty of the cases exhibited this finding.

The incomplete right bundle branch block pattern was present in four of the cases. In three of these the volume of left-to-right shunt was equal to 50% or more of the total pulmonary flow. Complete right bundle branch block was present in one case.

Evidence of right atrial hypertrophy was seen in nine of the patients, all of whom had marked pulmonary hypertension. Left atrial hypertrophy of the P-mitrale type * was seen in four of the patients and was always associated with a large left-to-right shunt. First degree atrioventricular block was seen in four patients. Figures 3-9 show

* P-mitrale type is a broad, notched P wave in Leads I and II with some left shift in the P axis.

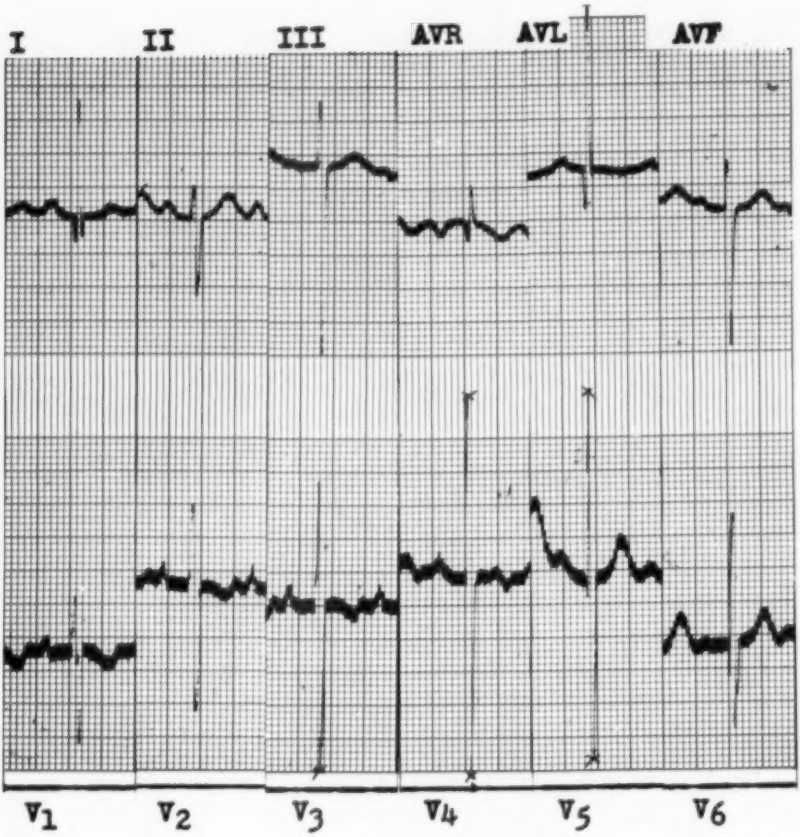

Fig. 6 (Case 6).—A 4-year-old girl with a large left-to-right shunt and normal right ventricular pressure. There is Grade II increase in voltage of the diphasic QRS in V_4, V_5. There is Grade II left ventricular hypertrophy manifested by marked left-axis deviation and a large qR in I, aV_L, V_6.

some representative electrocardiograms from this series.

Comment

Our data would indicate that the electrocardiogram in ventricular septal defect correlates reasonably well with the observed physiologic alterations. Pulmonary hypertension of major degrees was always associated with right ventricular hypertrophy. In the presence of significant left-to-right shunt and slight pulmonary hypertension, left ventricular hypertrophy, often with large diphasic precordial complexes, was usually found. The evidences of left ventricular hypertrophy tended to persist with increasing pulmonary artery pressure until the volume of left-to-right shunt became less than 20% of the total pulmonary flow.

Large diphasic precordial complexes were present in 30 of the patients, and their association with evidence of left, right, or combined ventricular hypertrophy is quite characteristic, though not specific, for ventricular septal defect. The infrequency of the incomplete right bundle branch block pattern is in contrast to the frequency with which we have observed this pattern in atrial septal defect and is somewhat contrary to the findings of Brink and Neill.[7]

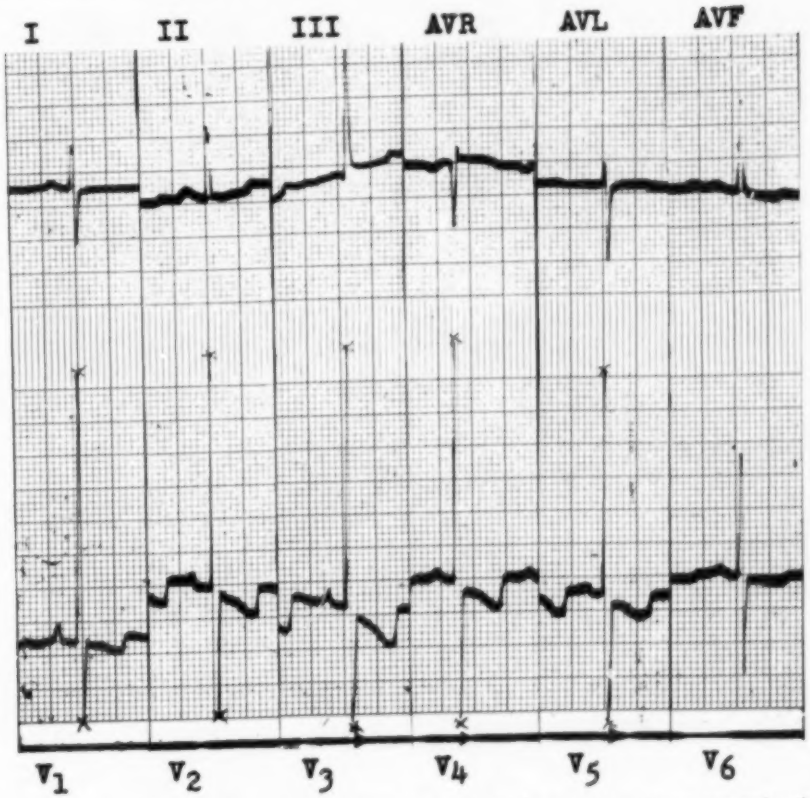

Fig. 7 (Case 50).—A 4-year-old girl with right ventricular systolic pressure approximating systemic and a moderate right-to-left shunt and no measurable left-to-right shunt. The electrocardiogram shows marked right ventricular hypertrophy manifested primarily by right-axis deviation and the very tall R in V_1. There is Grade II increase in the voltage of the diphasic QRS in V_4, V_5, V_6. There is Grade I right atrial hypertrophy manifested by a peaked P in V_1.

Our observations are similar to those of Marsico and associates,[5] although, contrary to their observations, we found little evidence of left ventricular hypertrophy as the volume of left-to-right shunt became small or disappeared in the presence of severe pulmonary hypertension.

Patent ductus arteriosus when associated with moderate pulmonary hypertension may produce combined ventricular hypertrophy in the electrocardiogram. However, the pattern of large diphasic precordial complexes is much less common in patent ductus arteriosus and the left precordial leads will usually show a qR in leads V_5, V_6 rather than the qRs with a deep Q wave. This is in accord with previous observations of Marsico and associates,[5] although we see occasional exceptions to this finding.

Evidence of atrial hypertrophy was not common in this series. Left atrial hypertrophy was occasionally seen with large left-to-right shunts, and evidence of right atrial hypertrophy was often seen in the presence of marked pulmonary hypertension.

Summary

A study of the electrocardiogram in 50 cases of ventricular septal defect is reported. There is generally good correlation between the physiologic abnormality observed at cardiac catheterization and the electrocardiographic findings.

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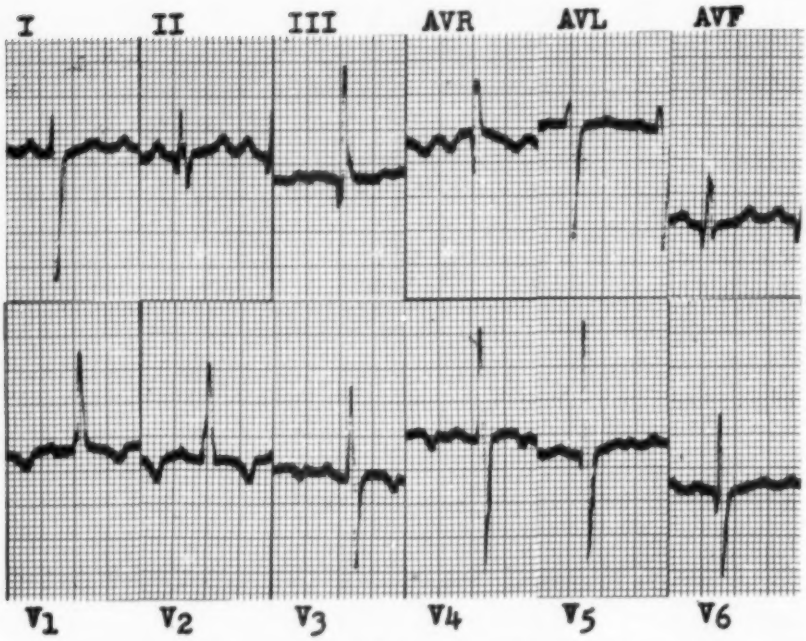

Fig. 8 (Case 48).—A 7-year-old girl with right ventricular systolic pressure approximating systemic and a moderately large right-to-left and no measurable left-to-right shunt. The electrocardiogram shows Grade III right ventricular hypertrophy manifested primarily by the tall R in V_1 and right-axis deviation in the frontal plane.

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Fig. 9 (Case 27).—A 6-year-old boy with moderately severe right ventricular hypertension and a large left-to-right shunt. These leads show wide notched P waves indicative of left atrial hypertrophy.

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Hypersymbiosis

Effects on Emotional Development

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Μηδὲν ἄγαν (Nothing in excess!)
Inscription at the temple of Apollo in Delphi

"Hypersymbiosis" is a poor word for a clearly defined phenomenon: a symbiosis between mother and child which is excessive and unduly prolonged. To think about this problem was occasioned by a recent experience. I was called to a 2¾-year-old girl with a febrile illness. The grandmother of this child is an analyst. The girl's mother had been analyzed three times during the past 10 years but still appeared to be neurotic. When she had her first child, she naturally tried to let the baby benefit from her knowledge and gains resulting from so much expenditure of time and money. She breast-fed the girl up to one year, using a self-demand schedule in its extremes. She was constantly with her baby and anxiously tried to avoid any frustration.

The child reflected her mother's anxiety. She was constantly demanding, exhausted her mother by clinging to her, and had shown sleeping disturbances since the age of 6 weeks. She cried every night until she was taken to her parents' bed. This developed into the distressing habit of not sleeping at all except with the parents; and even there only for short naps, interrupted by disturbing wakefulness which served to reassure the child of her parent's presence. During daytime, the girl would watch every move of her mother and go into a rage whenever she left the room. Both parents looked drawn and exhausted from lack of sleep. They were irritated at the child but did not admit it.

The father played a secondary rôle. He was silent and dejected and had no say in the child's rearing, since he had not been analyzed. To better the financial situation he went on long business trips, which the mother blamed for the child's difficulties. One wonders why the father stayed away for such long periods.

At 2½ years the girl had been taken to a kindergarten. This was obviously too early for a child so immature but was thought to relieve the home tension at least for a few hours daily. It proved a failure. Her mother had to stay with her all the time. The girl did not join the group but stayed with her mother in a corner where the home situation repeated itself in a changed environment. On the way to and from the nursery school, she dragged along her mother's blue nightgown which had been her constant fetishistic companion for over a year, day and night.

For a long time I had been unable to examine this child. She looked thin, emaciated, and unhappy. One day in my office she was as negativistic, destructive, and violent as ever. To the mother's surprise, she calmed down when I gave her an injection of poliomyelitis (Salk) vaccine. Facing this painful reality, this *roche de bronze* in a white coat, she suddenly seemed to feel more secure. From that day on, we have had a good, almost affectionate relation. The unflinching performance of an injection may well have represented the girl's first experience of firmness and discipline. It had such a surprising effect, since it fulfilled an important need of a child of this age, a

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need hitherto neglected and unrecognized by her mother.

Previous attempts to change the mother's attitude to her child had not only failed but were met with a hostile reaction to my "old fashioned ideas." Nevertheless, I used every contact with the child to improve the situation, mainly by setting an example. Soon, the mother recognized the good influence of my fearless approach and kind firmness, and, by subconscious identification, the mother changed her own attitude. The child became happier and more cooperative. In the past she had cried all the way to my office; she cried now when she had to leave it. She adjusted to kindergarten and no longer insisted on her mother's presence. Her sleeping improved as her anxiety decreased.

Every pediatrician has had similar experiences. We have the rare opportunity to observe such an adverse mother-child relationship from the onset and to follow its effects on the emotional development of these children. As years go by, some of these children become parents and bring their babies to us, thus extending our observation period well into their adult lives. We also can see how these young parents reenact their own childhood experience by repetition or avoidance.

The causes which lead to hypersymbiosis are manifold. A mother may be insecure and make her child dependent to increase her own feeling of security. She may feel incompetent as a mother and double her efforts to overcome this fear. She may try to make up on her child for what she was missing in her own childhood; or she may identify herself with her mother, who had the same overprotective attitude to her. Marital dissatisfaction, maladjustment to her life situation, or neurotic constriction of interests may make a mother concentrate all her life and affection on the child. Hypersymbiosis may be an overcompensation for lack of true affection or an appeasement of guilt feelings over rejection of the child. A mother may simply be confused by too much reading, misunderstand or exaggerate psychoanalytic or other principles in child rearing, and lose her common sense and empathy. She may fail to adapt her attitude to the changing needs of the growing child. Loss of a previous child or a late coming child of a mother in advancing years may be factors in establishing an excessive and prolonged symbiotic relation. It can be seen that anxiety plays a leading rôle in the genesis of hypersymbiosis.

It is also evident that cultural influences, social structures, and racial characteristics are of importance. The cool pathos of distance between persons prevalent in England but uncommon in America, may modify the mother-child relationship. Competitiveness in general and between the sexes, multiple choices in our civilization, tension and anxiety which prevail in American cities but barely exist in Swiss villages may be expected to influence all human relations but mainly that between mother and child.

When a child is born, the parasite-host relation of pregnancy is replaced by a symbiotic relation between mother and child. The infant depends on his mother for gratification of his basic needs, while the mother depends on the infant for satisfaction of her maternal instincts. A favorable balance or adverse imbalance in this mutual gratification may result, depending on maternal attitudes as well as on the infant's reactions. A child is born with an innate drive to mature and to gain independence. Out of a germinal state this drive grows into a strong force with the aim to develop into an integrated person or—to use Henrik Ibsen's word—to become "what the Master intended him to be."

An anxious mother will be frightened by every move of the child into freedom. Basically afraid of losing her child, she will misinterpret such moves as dangers to the child himself, transmitting her own anxiety to her offspring. Subconsciously serving her own needs, she will depict the world to her child as a plain of mortal dangers from which she alone is able to protect him. In

his induced, growing anxiety, the child readily accepts his mother's representation of the world and willingly submits to her overpowering administrations. Depending on his ego strength, the child may submit entirely, lose his initiative, and become dependent; or remnants of his drive for freedom and self-personification may turn resentfully against his overwhelming mother, resulting in hateful dependency. This component of hatred may be his main resource for gaining later emancipation, but may also leave a scar and pattern later human relations.

It is not intended to go into all facets of emotional disturbances resulting from hypersymbiosis. We see them at all ages from infancy to the late years, which proves that one does not simply "grow out" of them. Basic effects are anxiety, ego weakness, and immaturity. In early childhood sleeping disturbances and eating problems are common. In later childhood a whole spectrum of behavior and personality disorders result from dependency, rebellion, or hateful dependency. Among adolescents and adults we find figures like Oblomov in Goncharov's novel, with paralyzed initiative, passivity, and indecision; those with such low tolerance for frustration that they wall themselves in, narrow their interests and actions to avoid frustration; persons who in spite of high intelligence always remain in a dependent position because they are afraid of independence; others who can not hold a job because of displaced rebellion against their superiors; those who do not develop physical skills, since their mothers conditioned them to stay away from "dangerous" activities. A wide variety of sexual disturbances may result from hypersymbiosis with prohibitive and coercive attention to areas such as masturbation or bowel functions. Fixation in earlier phases of sexual development may ensue, and sexual maturity may never be attained.

We learned from observations of René Spitz [1,2] and others [3] the detrimental effects of emotional starvation in infancy. We see here that the opposite extreme, attempts at complete satisfaction of basic needs and anxious avoidance of frustration, may have equally bad effects. As Anna Freud [4] pointed out, it is actually impossible to avoid all frustrations. And even if we could we would not prevent neurosis. Need satisfaction comes rarely without delay, nor does it come in the way the infant wants it. Feeding on demand does not fulfill all needs, nor does any other single principle do so. The infant will blame his mother for anything that goes wrong, any delay in need fulfillment, in spite of all her anxious efforts to avoid them. These constant anxious efforts seem to do the harm. It is like giving one dose of anxiety with each dose of gratification, leaving the child tense, anxious, and constantly demanding without ever being satisfied.

Unavoidably, there is satisfaction and frustration in an infant's life. The relationship and balance between both seems to be important for normal emotional development. Some mothers find instinctively the right balance while others fail as a result of their own imbalance and anxiety.

The mother means the world to the young infant. As a good host she must guide this new guest into the real world and represent life with its vicissitudes of happiness and sorrow. In this we can help her if we are able to relieve her anxiety.

25 Central Park West (23).

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A Simple Method to Obtain Venous Blood Samples from Premature and Newborn Infants

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Obtaining venous blood samples from premature and small infants by the usual methods using the external jugular, the internal jugular, the femoral, or other peripheral veins most of the times is difficult and not without risk. We faced this difficulty at the start of our studies on blood coagulation in the newborn [1] and in the premature.[2] This led us to search for a modification of available procedures which would eliminate some of the existent difficulties. A modification of the Gardner-Murphy technique [3] adapted for drawing venous blood samples was investigated and after suitable changes found very satisfactory. Up to now more than 300 samples have been obtained from newborn and premature infants with this procedure which has been found simple and safe.

Material (Fig. 1)

1. Test tube graduated up to 5 ml.
2. Rubber plug to be adapted to the test tube.
3. Thirteen-gauge needle.
4. Polyethylene catheter number PE-60 or PE-100 about 20 cm. long.
5. Gardner-Murphy type needles, 19, 20, or 21 gauge, about 2 cm. long.
6. Twenty-gauge needle.
7. Plastic needle adapter.
8. Rubber tube.
9. Rubber bulb syringe.
10. Mosquito forceps.
11. Clothespin clip.

Perforate the rubber plug with the 13-gauge needle. Insert the polyethylene catheter through this needle leaving about 1 cm. of the catheter beneath the rubber plug. Withdraw the needle. This will leave the polyethylene catheter inserted through the rubber plug. Insert the rubber plug with the polyethylene catheter into the test tube. The 20-gauge needle is placed in the plastic adapter, this is connected to the rubber tube, and the rubber tube is connected to the rubber bulb. Perforate now the number 20 needle through the rubber plug. This simple system is made in order to obtain a mild negative pressure inside the test tube.

Procedure

Once the sterilization of the Gardner-Murphy needle has been performed, it is attached with a Mayo or mosquito forceps. The rubber bulb is compressed to its maximum and the rubber tube is clamped (Fig. 2). The skin is punctured on one side of

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From the Premature Service of the University Hospital, General Calixto Garcia.

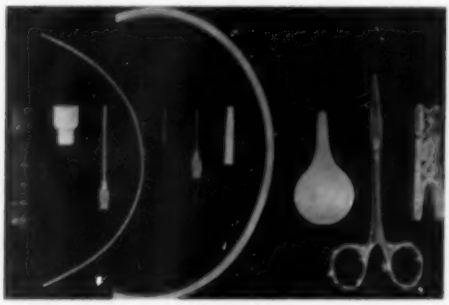

Figure 1

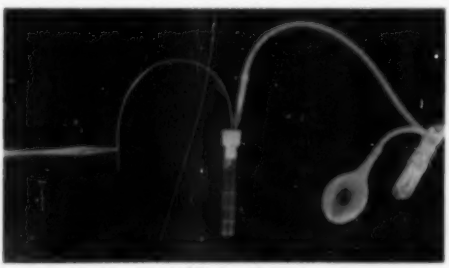

Figure 2

the vein; after this is done the clip is released and then the needle introduced in the vein. As the vein is entered, blood flows through the polyethylene catheter and soon begins to fall in fast drops through the tube (Fig. 3). For Gardner-Murphy needles gauge 19 we use a polyethylene catheter number PE-100. In the case of Gardner-Murphy needles gauge 20 or 21, catheter number PE-60 fits better. We always use the small scalp veins of the front or temporal region which can be easily exposed after shaving the head of the infant.[4] Other available peripheral veins may be used. If blood does not come out fast enough, mild pressure of both jugular veins will increase the flow. Proper position of the needle is important, and the operator should place it in such a way that the flow is quicker. Veins should be punctured against the blood flow which can be easily recognized by finger pressure. If more than one blood sample is desired, the test tube can be changed, but the rubber bulb must be compressed again between the change. We have found very convenient the use of a sphygmomanometer rubber bulb with its valve inverted which eliminates the clothespin, and, in the case of air leaking, the rubber bulb can be compressed again at any time. Siliconization of the whole system helps prevent clotting.

Figure 3

Comment

This method offers the following advantages:

1. It is easy to perform and learn without risk to the patient.
2. It completely eliminates hemorrhage.
3. There is absence of trauma to the premature as compared with the other methods.
4. Plasma is obtained without hemolysis.
5. It averts siliconization of syringes.
6. It is economical, since it eliminates expensive breakage of syringes.

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A Case of Phenylketonuria with Borderline Intelligence

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Phenylketonuria (phenylpyruvic oligophrenia), an hereditary molecular disease in man, is important as a type of mental deficiency whose genetics and biochemistry are sufficiently well-understood to indicate rational approaches to therapy. The condition is transmitted by an autosomal recessive gene which produces no known related mental signs in the heterozygous carriers (e. g., the parents of these patients).[1]

The affected persons lack activity of a liver enzyme which normally oxidizes phenylalanine to tyrosine.[2] As a result, from birth, dietary phenylalanine accumulates at high levels in the blood and is converted to an abnormal metabolite found in the urine, phenylpyruvic acid. These two findings establish the diagnosis. The mental deficiency, typically of severe degree, is thought to be secondary to the accumulation of phenylalanine or its abnormal metabolites. This hypothesis is currently being tested by treatment with low phenylalanine diets.[3]

The present paper describes an otherwise typical case of phenylketonuria with near-normal intelligence whose diagnosis has been carefully documented. The existence of such cases has been reported but not established rigorously.[1,4-6] The present patient is one of two sisters with similar biochemical disturbances, one of whom is severely retarded and the other only mildly so and able to function in society. These findings raise the possibility that the incidence of the disease (1 in 25,000 to 1 in 40,000 in the population) calculated from the number of institutionalized cases [1] may be too low. The existence of such cases also jeopardizes any conclusion based on a small number of children that a given therapy improves the mental status in phenylketonuria if the effect of treatment is evaluated by comparison only with the development of the more usual phenylketonuric patient. Identification of the conditioning factors which permit the development of near-normal intelligence in these exceptional patients may augment the present therapeutic efforts.

Report of a Case

The patient was a 13-year-old school girl examined, along with some 30 other apparently normal relatives of known phenylketonurics, for chemical evidences of heterozygosity.[7] All appeared superficially to be of average intelligence and, with the exception of the present patient, exhibited no gross disturbance of phenylalanine metabolism. Large amounts of phenylpyruvic acid in the urine and a fasting plasma phenylalanine level of 1.80 μmols per milliliter (29.7 mg. per 100 cc.) established the diagnosis of phenylketonuria in this girl.

Family History.—The family consisted of the parents and three children, all of whom were examined. There was no known consanguinity and no known cases of phenylketonuria or mental deficiency among the antecedents.

Father, 44, was a skilled electrician and mechanic. He was of average intelligence, and had earned a satisfactory living all his life.

Mother, 45, was a housewife. She was a social leader in the small town in which they lived and

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TABLE 1.—*Clinical Data*

	Subject of Present Report	Institutionalized Sister
Past History		
Pregnancy and birth	Normal	Normal
Major illnesses or injuries	None	None
First sat alone	6–7 mo.	Over 1 yr.
First walked	15 mo.	At 4 yr., but still only with support at 18 yr.
Speech development	Words at 12 mo., sentences by 24 mo.	Never spoke
Eczema	Never	Onset at 5 mo., severe until 12 mo., still intermittent at 18 yr.
Convulsions	Never	Never
Present Status		
Age	13 yr.	18 yr.
Height	5 ft. 8 in.	4 ft. 10 in.
Weight	135 lb.	86 lb.
Head circumference	21 ½ in.	21 in.
Hair color	Dark blonde	Formerly blonde, now light brown
Eye color	Blue	Blue
Activity	Mildly immature and socially insecure, but competent	Sedentary; noisy, untidy; masturbates; injures self; requires restraint
Hand postures	Repetitively crosses and uncrosses middle fingers	Constant aimless activity and gesticulation
Speech	Mildly immature, many stock phrases; articulation normal	None
Neurological examination	Normal except slightly exaggerated knee and ankle jerks	Knee jerks markedly exaggerated, ankle jerks slightly so
Mental age and I. Q.	M.A.: 9 4/12; I.Q.: 69 (Binet) I.Q.: 78 (Wechsler)	M.A.: 5 mo.; I.Q.: 4
Electroencephalogram	Borderline—Figure 2	No abnormalities in rather unsatisfactory tracing

belonged to numerous committees in the church and school. She was head of a recent fund drive in her area.

Brother, 18, was recently graduated from high school, where he was president of his class. His schoolwork was above average. He preferred to work with his hands rather than to read. He had restored several antique automobiles and built model airplanes.

Sister, 17. The diagnosis of phenylketonuria was established at an early age on the basis of mental retardation and excretion of phenylpyruvic acid. She had been institutionalized at the Wrentham State School for the last 10 years. Her present I. Q. was less than 10. The diagnosis was confirmed by an elevated plasma phenylalanine level and excretion of phenylpyruvic acid (Table 3).

Present case, 13. A positive ferric chloride test for urinary phenylpyruvic acid was noted in an examination at the Children's Hospital, Boston, at age 7, at which time she was having difficulty in school.

Past History and Present Status.—These data are summarized in Table 1, where similar data for comparison are also given for the institutionalized sister of the patient.

School Reports.—Abstracts of the school records and tests show the patient's progress and the evaluations of her by different persons (Table 2).

Psychological Evaluation.—An abstract of the psychological report is as follows:

On the Stanford-Binet, the patient achieved a mental age of 9 years 4 months. She obtained a basal age at year VII with some successes through year XIII. Her vocabulary level was at year XII,

TABLE 2.—*School Reports*

School: Began kindergarten at 4 10/12, first grade at 5 10/12; repeated first and fourth grades, now in sixth, having trouble; child disturbed by this, says "why am I so dumb when everyone else is smart?"; unhappy and worries a lot; plays piano fairly well; socially more at ease with Junior High School children, because of large size, but is careful to conceal from them where she goes to school; begins to be interested in boys, under watchful eye of mother

School Marks:

Grade	Reading	Language	Spelling	Arithmetic	Writing	Music	Art	Geography
1st–1948	D	D	D	D	D			
1st–1949	D	C	C	D	D			
2nd	C	C	C	D	C	B	B	
3rd	C	C	C	D	D	B	B	
4th–1952	D	D	C	D	D	C	C	D
4th–1953	D	C	C	D	C	B	C	C
5th	C	C	B	D	B	B	C	D

School I. Q. Tests:

M.A.	5-8	9-6	8-10
C.A.	6-4	13-0	13-5
I.Q.	89	73	73

Teachers' Comments: (all May, 1956)

Evokes comments from strangers because of appearance
No interest in group activities; lacks aggressiveness
Comments frequently about "nervous" feelings
Has no friends; seems unaware of other people except in audience capacity
Completely passive
Gullible
Complete isolation; playground activity involves either standing alone in a corner or aimlessly pacing the yard
(The patient's behavior seems quite different in the presence of her parents or when seen socially or professionally, than it is described in the presence of school tension—Authors)

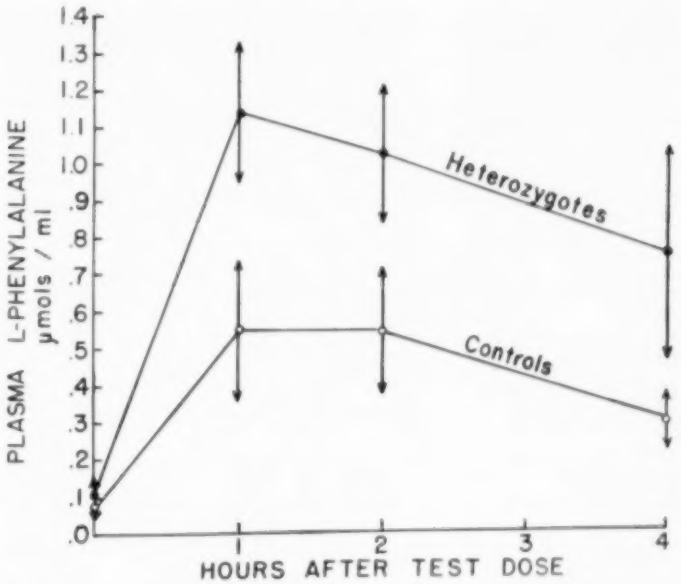

Fig. 1.—Plasma L-phenylalanine levels in normal (-o-) and heterozygous (-•-) persons following oral doses of 0.1 gm. L-phenylalanine per kilogram body weight. Each line represents the mean value from 19 persons. The length of the arrows represents one standard deviation above and below the means.

with words being defined at a concrete level. She was more successful when given performance items from the Wechsler Intelligence Scale for Children, which revealed an I. Q. of 78. She was able to read quite well but had difficulty in comprehending or remembering. Her parents mentioned this in their discussion of her school work. Her ability to abstract in a meaningful way was poor.

She reportedly played the piano, occasionally playing for her girl scout troop. She was cooperative throughout the session, at times giggling somewhat inappropriately.

Chemical Studies.—In addition to the determinations by specific methods of phenylpyruvic acid in the urine and phenylalanine in the plasma, the other abnormal urinary metabolites characteristically found in this disease were determined. Phenyllactic acid,[8] *o*-hydroxyphenylacetic acid,[9] indolelactic acid, indoleacetic acid,[10] and phenylacetylglutamine[10] were determined by the methods cited. All of these were present in the urine of the patient in the amounts usually found in phenylketonuria. All members of this family were given phenylalanine tolerance tests,[7] by which it is possible to distinguish on a chemical basis the normal persons and the apparently normal heterozygous carriers, as well as the phenylketonurics. After an oral dose of L-phenylalanine, the heterozygotes have plasma phenylalanine levels during the four-hour test period approximately twice those seen in normal persons (Fig. 1). Less than 15% of persons so far examined gave indeterminate results in the overlapping region between the two groups (Table 3).

TABLE 3.—*Chemical Measurements*

	Urine Phenylpyruvate* (Mg/Mg. Creatinine)	Plasma Phenylalanine† (μMols/Ml) Fasting	Plasma Phenylalanine† (μMols/Ml) Four Hours After 0.1 Gm. L-Phenylalanine per Kilogram of Body Weight
Father	0	0.11	0.75
Mother	0	0.11	0.62
Brother	0	0.12	0.57
Sister	0.53	2.34	----
Patient	1.05	1.81	----
Control Series‡			
Normal	0	0.07 (0.04–0.10)	0.30 (0.21–0.50)
Heterozygotes	0	0.10 (0.06–0.15)	0.76 (0.45–1.62)
Phenylketonurics	0.85 (0.5–1.5)	1.70 (1.52–2.73)	----

* Determined by the ferric citrate method of Kropp and Lang.[11] The amounts and identity were confirmed by formation of the enol borate complex (Knox and Pitt[12]).
† Determined by the specific bacterial decarboxylase method of Udenfriend and Cooper.[13]
‡ Values represent the means and ranges (in parentheses) observed in groups of 19 adult persons.[7]

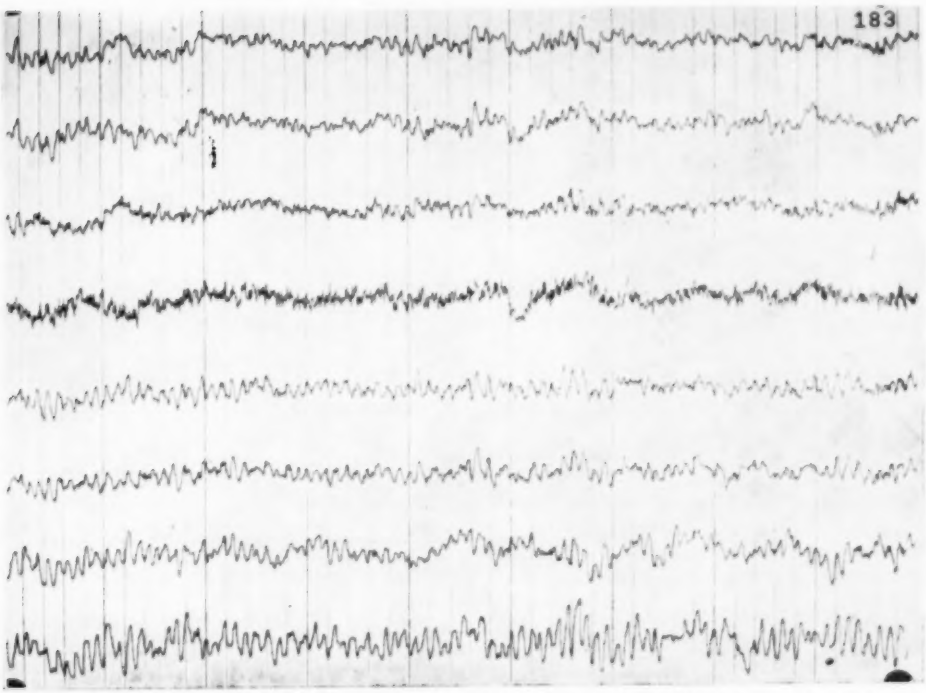

Fig. 2.—Electroencephalogram of the subject of the present report, which is normal except for borderline spiky activity in the right occipital (bottom) lead.

The chemical measurements made on the members of the present family, including the phenylalanine tolerance test results, are summarized in Table 3. From these data it is clear that both parents were heterozygous for the phenylketonuria gene, as was expected, that the brother was probably also heterozygous, and that both the patient and her institutionalized sister were homozygous for this gene. The amount of phenylpyruvic acid excreted (per milligram of urinary creatinine) and the fasting levels of plasma phenylalanine found in these two homozygotes were within the usual ranges given in Table 3 for our series of over 30 patients. There was no indication of a metabolic disturbance of a lower degree in the more intelligent sister.

Comment

The mental deficiency in phenylketonuria is usually of a severe degree, and at least some degree is believed to be invariably present. A compilation of psychometric studies on 330 patients reported in the literature or observed by Jervis [1] showed the largest group to have I. Q.'s less than 10 (37%) and 94% to have I. Q.'s less than 50, but the distribution curve was skewed in the direction of normal intelligence. Four patients were said to have I. Q.'s between 61 and 70, and three had I. Q.'s above 70 (0.9%). The latter three cases are presumably similar to the present case and are included in those described below. Instances of such borderline intelligence among phenylketonurics have always been viewed with skepticism, even by those reporting the cases.

Cowie [4] reported first seeing a child with phenylketonuria at 3½ years of age because of a burn. At that time he seemed somewhat backward, was able to speak only a few words, and was classified as an imbecile. He was seen again at 7 11/12 years of age and was found to be "extremely shy, refusing to talk to adults whom he does not know well." His I. Q. was 76 by the Stanford-Binet test, and 90 by the Porteus maze.

His urine showed a positive green color when tested with 5% ferric chloride and was found to contain 500 mg. of phenylpyruvic acid in 24 hours by the 2,4-dinitrophenylhydrazine method[8] (a typical amount for a phenylketonuric child in our experience). Other members of the family were reported to be normal. Cowie felt that the biochemical error might be incomplete or in some way compensated and that a certain amount of phenylalanine could follow the normal pathway of metabolism.

Brugger's[5] patient was a brother of the patient with phenylketonuria found in a survey of 1634 institutionalized defectives in Switzerland. That patient, a 15-year-old girl, was a low-grade imbecile and in every way clinically typical of the usual institutional phenylketonuric. Her 12-year-old brother, however, scored an I. Q. of 85 on the Binet-Simon test. He had repeated one grade in school and was still doing below average work. His motor function was described as rather stiff and awkward, and his posture was described as slumping forward. He was apparently nevertheless a competitive member of the community, albeit probably with some concessions. The phenylpyruvic acid content of this boy's urine was 31 mg. per 100 cc., and the ferric chloride test on it was positive.

Jervis[1] referred to another case personally observed, a boy with an I. Q. of 86 whose phenylketonuric sister had an I. Q. of only 20. Two relatively high-grade phenylketonurics in a family were observed by Yannet,[15] who supplied the following details:

> The mother was dead and it was not possible to obtain a history of consanguinity in her marriage. There were 3 full siblings and 4 half-siblings, full siblings in 1947. One sister was 24 years old and her urine was negative for phenylpyruvic acid, since the father married a second time. We had an opportunity to check the urines of the three. She was of normal intelligence. Another sister was 22 years old. Her urine was positive for phenylpyruvic acid. Although a formal psychological test could not be carried out since she refused to cooperate, it was my impression in talking with her, that she was probably of high grade moron or borderline intelligence. She was working at a supervised and simple occupation and was giving no difficulty at home at that time. The brother was 18 years old and showed no phenylpyruvic acid in the urine and was of dull normal intelligence. Four half-sibs were not seen. The father was not seen because of having moved to a distant state. From the description of his occupation, I would guess that the father was of average normal intelligence. The mother could not be evaluated from the history but, obviously, was not defective.
>
> Our patient, a man of 29, had numerous psychological studies during his 15 years in the Southbury Training School. His last study was at age 27, at which time he obtained a score of approximately 90 on the Wechsler-Bellevue test. On the basis of many of the other tests, he was diagnosed by our psychology department as of dull normal intelligence. He had one mental testing just prior to admission to the institution in 1941, of 65 on a Stanford-Binet. I am sure that represented the effect of emotional difficulties in the community since he was transferred to us from a reformatory where he had been placed two years previously because of his asocial behavior. At the present time, we have difficulty in placing this boy out, even though his I. Q. is as high as it is because of personality difficulties and lack of special home facilities.

Dr. Yannet kindly allowed one of us to examine this patient at the Southbury Training School. He is blond, blue-eyed, well-developed and nourished and presents no obvious abnormality of any kind. Physical and neurological examinations were negative. He works in the stock room in the training school.

Another patient, with the slightly lower I. Q. of 69 (Wechsler-Bellevue), was reported by Cohen and Kozinn.[6] This person worked steadily as a presser of gloves and was able to support a family of a wife and two children. One child was also a phenylketonuric. Both diagnoses were based only on urine ferric chloride tests. The authors suggested that the father might be a "forme fruste" of phenylketonuria, and that the presence of the disease in both father and child might indicate a different mode of inheritance in this family. It is more probable, however, that the father was homozygous and the mother heterozygous.

The present case demonstrates that the typical homozygous form of phenylketonuria

may be associated with borderline intelligence and so lends credence to the less completely studied cases above. She exhibited the classical chemical findings of the disease from an early age, and the degree of metabolic disturbance was comparable to that of her severely affected sister. The usual recessive mode of inheritance established for phenylketonuria is most probable, since both parents were directly shown to be heterozygotes, as was the brother, while she and her sister were homozygotes. The possibilities of an incomplete biochemical error in phenylalanine oxidation, heterozygosity, "forme fruste," or homozygosity with incomplete penetrance, which have been postulated to explain such cases, are not compatible with the chemical evidence.* Her intelligence is less than average, near the lower limits of the normal range, and less than that of the unaffected members of her family, but it is far superior to that of her affected sister and to that usually seen in phenylketonurics. There is no evidence now available that the disease is compatible with completely normal or above normal intelligence.

The incidence of such cases is probably not so large as the discovery of one among some 30 heterozygotes might indicate. In a survey of noninstitutionalized persons Jervis did not find any persons excreting phenylpyruvic acid among 10,000 soldiers examined.[1] Larsen found no phenylketonurics among 8220 apparently normal persons in Sweden.[16] But the lower limit of frequency should be represented by Jervis' series from institutionalized populations, with about 0.9% of phenylketonurics (the cases cited above) who would be considered in the high-grade category. These persons frequently escape being institutionalized, however, as did the present case. It is therefore most likely that additional cases will be found in families known to contain phenylketonurics and among persons of low-normal intelligence from unsuspected families who have some difficulty in school or life.

The large variation in intelligence met with among phenylketonurics showing similar kinds and degrees of chemical disturbance, provides indirect support for the belief that the loss of enzyme activity is the primary defect in this disease. Mental deficiency together with blondness of hair, blueness of eyes, tendency to have eczema and to have electroencephalographic abnormalities and seizures are secondary results of the primary chemical disturbance and vary more widely in different persons than do the chemical derangements.

There was a severely affected person in this and in three other families with such high-grade phenylketonurics. These cases seem to eliminate the possibility that the relatively high intelligence of one person in the family is referable to a variant gene in these families. No striking clinical or chemical characteristic which might explain her relatively superior mental development was found in the present patient. The possibility that the toxic effect of phenylalanine can be conditioned by other genes or environmental influences remains to be tested. The nature of the deleterious effect of phenylalanine, if one exists, must be identified. The existence of such cases showing unusual mental development while having typical high phenylalanine accumulations points to the possible future discovery of new avenues of therapy in addition to the prevention of high plasma phenylalanine levels by low-phenylalanine diets, which is currently being tested.

Until now, it has been assumed that all or nearly all phenylketonurics were mentally deficient and retarded in development. However, since some persons may spontaneously develop almost normally, encouraging results must be found in a number of persons with a given therapeutic regimen before it can be

* Two additional phenylketonuric patients with near-normal intelligence, a 2½-year-old girl with I. Q. 82 and a 50-year-old man with I. Q. 67, have recently been reported (Lancet *2*, 917, 1956). The blood levels of phenylalanine and urinary levels of phenylpyruvic acid in these patients, while thought to be low, were not definitely outside the usual ranges observed.

judged of value. The evaluation of therapeutic trials would be greatly improved if conducted in comparison with an untreated control population and against a statistically known background of the natural history of this disease in untreated persons. Such information has not previously been of great moment and is not available in the literature. In the absence of such background data, improvement must be measured in relation to the mental status of the same person before treatment, and this can be less accurately determined in the youngest and most suitable patients.

Summary

The case of a 13-year-old phenylketonuric girl with borderline to dull normal intelligence is reported. She had an 18-year-old institutionalized phenylketonuric sister whose I. Q. was most recently estimated at 4. The subject of the present report, who was discovered in the course of a survey for heterozygotes in relatives of known phenylketonurics, was in the sixth grade and scored an I. Q. of 78 by the Wechsler method and 69 by the Stanford-Binet. Her plasma phenylalanine levels, and urinary excretion of phenylpyruvic, phenyllactic, *o*-hydroxyphenylacetic, indolelactic, and indoleacetic acids and of phenylacetylglutamine were all in the range usually observed in patients with phenylketonuria.

This case lends support to the existence of phenylketonurics with near-normal intelligence, of whom at least three have already been reported in the literature but less completely chemically and psychologically documented. The existence of cases in this intelligence range suggests the need for great caution in evaluating effects of diets low in phenylalanine or other experimental treatment of the disease.

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The psychological testing of the subject of the present report and of her institutionalized sister were carried out by Amelia Blackwell, M. A.

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The Sweat Test in Cystic Fibrosis of the Pancreas

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Introduction

In 1953 di Sant'Agnese et al.[1,2] described a new diagnostic test for cystic fibrosis of the pancreas. This test was based on their discovery that the Na and Cl concentrations in sweat of patients with this disease is usually significantly higher than in normal persons and higher than in patients with a variety of other diseases. In the meanwhile other groups of investigators [3-5] came to the same conclusion.

The object of this article is

1. To examine whether a difference exists in the sweat-excretion rate at different places on the abdomen.

2. To compare the concentrations of Na and Cl in the sweat at these places and to determine whether there are extreme variations in concentration which would affect the value of the sweat test.

3. To compare our results of sweat analysis of patients with cystic fibrosis of the pancreas, of relatives of these patients, and of a number of controls with those of other investigators.[1-6]

4. To discuss the diagnostic value of this test.

Selection of Cases

The sweat test was carried out on persons falling into three groups:

Group 1 (Controls).—This group consisted of 45 patients on the wards of the Pediatric's Clinic in Leiden, with a variety of illnesses, e.g., celiac disease, chronic pulmonary and kidney diseases. Included are some patients who had recovered from an acute disease. Patients with cystic fibrosis of the pancreas and any of their relatives were excluded from this group.

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Group 2.—This group consisted of 23 patients with cystic fibrosis of the pancreas (from 3 months to 16 years of age). Twenty-two of these showed the clinical and laboratory findings of cystic fibrosis of the pancreas. The oral gelatin loading curve[7] was abnormal in all of them, and the trypsin activity found in the duodenal fluid was absent or very low.

The one other patient (Patient 23, girl, 9 years old) had a normal or slightly reduced trypsin activity in the duodenal fluid, a normal gelatin loading curve, a normal reabsorption coefficient of fat, and an increased viscosity of the duodenal fluid. She had, however, some of the features of cystic fibrosis of the pancreas, bronchiectasis on both sides with severe respiratory involvement (Bacillus pyocyaneus). Her sister had died as a consequence of this disease. Her sweat test appeared to be pathological. It is possible that this child belongs with Group 3.

Group 3.—This group consists of 12 relatives (7 adults and 5 children) of the patients in Group 2. None of this group had any complaints, although two of them suffered from regularly recurring colds.

None of the subjects in any of the groups was treated with corticotropin (ACTH) or desoxycorticosterone acetate (DCA) and none were acutely ill or febrile at the time of this examination.

Methods

Sweat was collected according to a slight modification of the method of di Sant'Agnese et al.[1] The patients were subjected to a mild thermal stress in a small room maintained at 29 C-32 C and a relative humidity of 50%-60%. For a sufficient sweat production it is advisable to use the higher temperature range. They were lying quietly on their backs for one and one-half hours. A few of them cried for a while. Food and fluid were not restricted.

The abdomen was washed well with distilled water and wiped off. Electrolyte-free gauze (washed several times with distilled water, wrung out, and dried) was cut into patches of ±40 sq. cm. (or ±25 sq. cm.[2]) and weighed in a stoppered glass container. The gauze was placed at three different sites on the abdomen: just above the umbilicus (A) and on the right (R) and left

(L) sides of the abdomen below the umbilicus. The patches were covered with a piece of impermeable plastic and sealed at the edges by adhesive tape. A towel was pinned around the abdomen, and the subjects were covered with a sheet and a blanket.

After a period of one and a half hours the tape was partly removed and the patches were taken off and rapidly placed into their respective containers and reweighed. The difference between the two weights gave us the volume of sweat. A determined quantity of distilled water, e.g., 20 ml., depending on the sensitivity of the Na and Cl determinations, was added and next day Na and Cl were determined in the eluate.

The Na concentration was determined with the flame photometer and the Cl according to a potentiometric titration method.[8] The reproducibility of both methods was about 3% when the quantity of sweat was higher than 0.250 gm. and the concentration of Na and Cl higher than 20 mEq. per liter.

Since the tests were performed at a room temperature which varied between 29 C and 32 C and a relative humidity between 50% and 60%, the results will be somewhat dependent on differences in temperature and humidity. These variations approximate the conditions much more, if this test is to be used as a routine method. The results, however, of comparative studies of the mean sweat excretion rate and of the mean electrolyte concentration, on similar areas of the abdomen, will be relatively little influenced.[4]

Results

1. *Mean Sweat-Excretion Rate (Table 1).*—Table 1 shows the results of the mean sweat-excretion rate at A, R, and L of 45 controls and of 23 patients with cystic fibrosis of the pancreas. Since there are no significant differences in the excretion rates of the sweat between these two groups, these data have been combined in the last column of this Table with their standard deviation, σ, and the standard deviation of the mean, σm.

On the basis of these results (Table 1) the following things are evident:

A. No significant difference exists between the *mean* sweat-excretion rate of the controls and of the patients with cystic fibrosis at the three respective sites of the abdomen.

B. There is no significant difference in the mean sweat-excretion rate between R and L in each of the groups.

C. In groups 1 and 2 the mean sweat excretion rate is significantly higher at site A than at R or L.

2. *Mean Na and Cl Concentrations of Sweat.*—The concentrations of Na and Cl were determined as described under Methods. From these analyses it was possible to conclude the following:

A. The mean concentrations of Na and Cl in the sweat of 45 controls from the areas R and L were not significantly different.

B. There was no significant difference between the mean Na and Cl concentrations in the sweat at R and L in 23 patients with cystic fibrosis of the pancreas.

C. In the 68 cases the mean concentrations of Na and Cl in the sweat obtained from area A was about 20% lower than that obtained from R or L. This is probably due to the larger sweat-excretion rate at this area (see under Results, 1C).

3. *Na and Cl Concentrations in the Sweat of Controls, of Patients with Cystic Fibrosis of the Pancreas, and of Their Relatives (Table 2).*—Table 2 summarizes the mean results of the analyses of the sweat of the three groups studied (see under Selection of Cases). In Figures 1 and 2 the distribution curves of the Na and Cl concentrations of the sweat of these groups are given.

TABLE 1.—*Mean Volume of Sweat Excretion During One and One-Half Hours per Forty Square Centimeters of Gauze on Sites R, L, and A*

Number of cases		45 Controls	23 Patients with Cystic Fibrosis of the Pancreas	68 Total of Both Groups
Sweat area:	R	0.347 ml.	0.317 ml.	0.337 ml.
	L	0.328 ml.	0.304 ml.	0.320 ml.
	A	0.512 ml.	0.544 ml.	0.523 ml.

TABLE 2.—*The Mean Concentrations of Na and Cl in the Sweat of the Three Groups Studied, with Their Standard Deviation, σ*

Group	Number and Kind of Subjects	Concentration in MEq. per Liter Na±σ	Cl±σ
1	45 controls	21.5±10	19.6±8.5
2	23 patients with cystic fibrosis of the pancreas	121±27	118±23
3	12 relatives of patients in Group 2	49.9±34	45.7±25

In Table 3 our electrolyte concentration findings are compared with those of other investigators.

Comment

It is evident from Table 1 that there is no significant difference between the mean excretion rate of the sweat of patients with cystic fibrosis of the pancreas and of the controls if the same parts of the abdomen are compared. Di Sant'Agnese et al.[1,2] Shwachman et al.,[3] Barbero,[4] and Mauer [5] came to the same conclusion. The absolute value of the sweating rate, however, depends on many variables (a. o. area of the body, temperature).

It was found in our work that site A of the abdomen (above the umbilicus) had a higher mean sweat excretion rate than site R or L and that the mean Na and Cl concentrations of this sweat was somewhat lower (±20%). Locke et al.,[9] on the other hand, described an increased Na and Cl concentration with an increasing velocity when taken from the same area on the arm.

It was evident from our study that the concentrations of Na and Cl in sweat obtained from the three different areas of the abdomen do not differ enough to affect the practical value of the "sweat-test" as a diagnostic aid in cystic fibrosis of the pancreas. This is due to the fact that the mean concentrations of Na and Cl in sweat of patients with cystic fibrosis appear to be several times higher than that found in the sweat of the controls (Tables 2 and 3 and Figs. 1 and 2). It is probable that the area of collection will have little influence on the value of the sweat test. This can be substantiated by comparing the values in Table 3 as well as by our comparative study on areas R, L, and A.

The mean concentrations of Na and Cl in the sweat of our controls (Table 3) are generally lower than those of the controls of the other investigators.

It is possible that this difference in Na and Cl concentrations of the controls is a.o. caused by the fact that some investigators did not use electrolyte-free gauze. We found on the average in ±40 sq. cm. hydrophilous gauze (Eshaco Perfect, Utrecht) about 0.0010 mEq. Na and 0.0015 mEq Cl. A low excretion rate of sweat, e. g., 0.100 ml. per one and one-half hours will cause a Na increase of 10 mEq. per liter and a Cl increase of 15 mEq. per liter. These values will be of higher percentage importance in

TABLE 3.—*Comparison of This Investigation with Those of Others*

Investigators	Ref.	Area of Collection	Mean Concentrations of Na and Cl in Sweat of Controls and of Patients with Cystic Fibrosis of the Pancreas: Controls Number of Cases	Controls MEq/L Na	Controls MEq/L Cl	Pat. with Cyst. Fibr. of Paner. Number of Cases	Pat. with Cyst. Fibr. of Paner. MEq/L Na	Pat. with Cyst. Fibr. of Paner. MEq/L Cl	Highest Values Found in Controls MEq/L Na	Highest Values Found in Controls MEq/L Cl	Lowest Values Found in 99 Cases of Cyst. F. of Pancreas MEq/L Na	Lowest Values Found in 99 Cases of Cyst. F. of Pancreas MEq/L Cl
di Sant' Agnese et al.	1,2,12	Abdomen or scapular region	226	52	27	140	133	106	80	60	80	50
Shwachman et al.	3,10	Back	33	30.5	35.3	58	119	130	60–70	..	70–80	..
Barbero et al.	4	Abdomen	31	25.8	36.0	10	166	172	88	93	111	116
Barbero et al.	4	Entire body	50	37.0	36.9	21	163	162	102	112	102	103
Mauer et al.	5	Abdomen*	38	..	21.3	18	..	128	..	50	..	90
Jaartsveld	6	Back	8	14.2	12.7	8	89	87	26.8	21	16.5	10.2
This investigation		Abdomen	45	21.5	19.6	23	121	118	56	43	78	79

* Sweat production by means of intradermal injection of a parasympathomimetic drug. Values obtained from a figure in the article. Controls were normal children.
Only 2 values between 50 and 60 MEq/L; 138 values higher than 60 MEq/L.

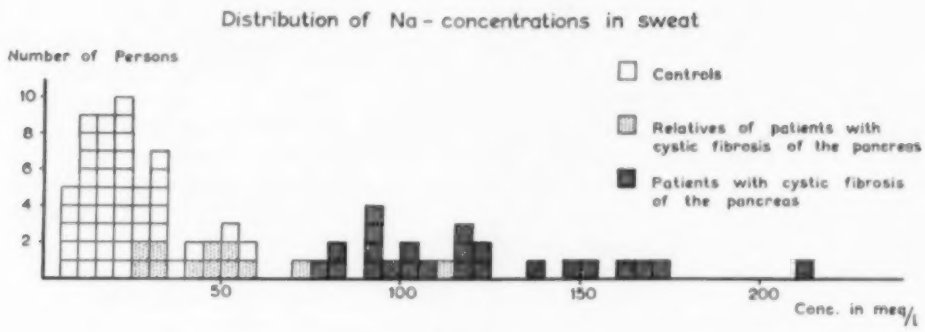

Figure 1

controls than in patients with cystic fibrosis of the pancreas.

It is also possible that the higher salt concentrations, found by the other investigators, are caused by a higher sweat-excretion rate [9] or by a chance selection of cases.

From the sweat analyses in patients with cystic fibrosis of the pancreas it is possible to conclude that in six out of the seven investigations (Table 3) the mean Na and Cl concentrations are considerably higher than in the controls. Moreover Shwachman et al.,[3,11] Barbero et al.,[4] Mauer et al.,[5] as well as we have found that there is no or very little overlapping in the Na and Cl concentrations between the controls and the patients with cystic fibrosis of the pancreas. Di Sant'Agnese et al.[1,2,12] also have found in 1956 less overlapping than in their original work (1953).

In 1954 Shwachman et al.[10] reported the results of two patients with pancreatic deficiency and pulmonary changes but with normal sweat electrolyte values. These authors, however, failed to describe these cases in their review article of 1955.[3] Recently di Sant'Agnese [12] described another one.

Combining the above-mentioned six investigations, it appears that in about 300 sweat tests, performed on patients with cystic fibrosis of the pancreas, 99% of (1) all the Na concentrations are higher than 70 mEq per liter; (2) all the Cl concentrations are higher than 50 mEq per liter. In 20 patients with meconium ileus, recently described by Shwachman et al.,[11] all had a pathological "sweat test."

Although Jaartsveld [6] found mean Na and Cl concentrations in the sweat of his eight controls which were nearly equal to our results, it is difficult to understand why four, out of his total of eight patients with cystic fibrosis of the pancreas, had Na and Cl concentrations in the sweat which were

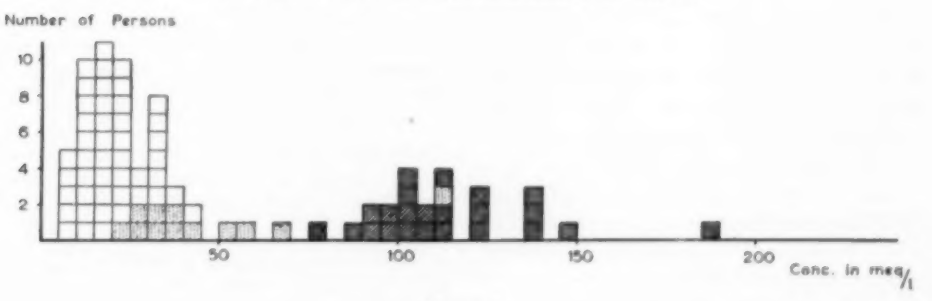

Figure 2

considerably lower than 70 and 50 mEq. per liter, respectively.

From Table 2 and Figures 1 and 2 it is evident that the mean Na and Cl concentrations of sweat of relatives of the patients with cystic fibrosis of the pancreas are higher than those of the controls. Some of the relatives have sweat electrolyte abnormalities similar to those of the patients.[3,5,11] Two brothers (1½ and 5 years old) of Patient 23 (see under Selection of Cases) had elevated concentrations of Na and Cl in their sweat. However, they had no complaints, and their gelatin loading curves were normal.

From this study it is evident that our results agree with those of other investigators.[1-5] It can be concluded from these investigations that the sweat test is of great diagnostic value since it has shown[13] the following:

1. In *all* patients with the anatomical changes of cystic fibrosis of the pancreas (at autopsy) the Na and Cl concentrations in the sweat were pathologically elevated.

2. In the studies made by the American investigators it has been discovered that in 99% of living patients, having the characteristic pulmonary picture of this disease and with a low or absent tryptic activity in the duodenal fluid, the Na and Cl concentrations in the sweat were pathological.

The composition of the sweat of all our 23 patients was abnormal (Table 3).

Summary and Conclusions

The sweat excretion rate was determined on three different sites of the abdomen in 45 controls and in 23 patients with cystic fibrosis of the pancreas. There was no significant difference between the mean excretion rates of the sweat in both groups.

The Na and Cl concentrations in the sweat were determined on three different sites of the abdomen in 45 controls, in 23 patients with cystic fibrosis of the pancreas, and in 12 relatives of these patients.

Together with the results of other investigations it is possible to conclude that the differences in Na and Cl concentrations in sweat, collected from different areas of the trunk, will have no great influence on the diagnostic value of the "sweat test" if the test is performed similarly in the group of patients with cystic fibrosis of the pancreas and in that of the controls.

In accordance with other investigations we found that no or little overlapping occurs in the Na and Cl concentrations of the sweat between controls and patients with cystic fibrosis of the pancreas.

Twenty-two patients, who showed the clinical and laboratory findings for cystic fibrosis of the pancreas had evidently elevated Na and Cl concentrations in their sweat. One patient with the clinical lung features for cystic fibrosis of the pancreas and with a family history of this disease had a normal trypsin activity of the duodenal fluid. The "sweat test," however, was pathological. In two of her five siblings this test was pathological as well, although none of them had complaints and their gelatin loading tests appeared to be normal.

"Cystic fibrosis of the pancreas" may occur in patients with a normal pancreatic function (See also 12).

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Afd. Kindergeneeskunde, Academisch Ziekenhuis.

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The Child as a Person Developing*

I. A Philosophy and Program of Research

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It is an honor to be given the privilege of presenting the Benjamin Knox Rachford Lectures. I am most appreciative of the honor as well as grateful for the opportunity of expressing a few of my thoughts concerning the child as a person in the process of becoming an adult. The reading of a number of Dr. Rachford's papers, with pleasure and profit, left no doubt in my mind that he, too, was vitally concerned with the importance of a person. I like to think that he would be in sympathy with my point of view, were he here tonight.

It seems like a very trite statement to say that, as physicians, we should always be concerned primarily with the child rather than the disease. Perhaps, however, each generation needs to reexamine this truism in the light of increased knowledge and understanding both of the nature of the human organism and of diseases. In my two lectures I shall be concerned chiefly with the reexamination of the nature of the child as he grows and develops from birth through infancy, childhood, and adolescence. As my title suggests, I shall stress the value of considering any given child at any age as a person—an individual human being—going through the dynamic process of becoming a mature adult.

Just about 200 years ago, on April 11, 1759, Philibert Gueneau de Montbeillard started taking a series of measurements on his own newborn son. He continued measurements and observations at regular intervals until this boy was 18 years old. These were published in Buffon's well known "Histoire Naturelle" in 1777. Buffon had many interesting comments to make about the nature of the curves of growth which were revealed by Montbeillard's data. In 1927 Richard Scammon republished the data under the title, "The First Seriatim Study of Human Growth." It is a temptation to tell you more about Montbeillard, who made significant contributions to ornithology, who innoculated this same son for smallpox 50 years before Jenner's famous experiment, and who apparently visualized the fascination of studying the pattern of the developmental pathway traversed by a human being in reaching adult life. It would be fun, too, to spend more time with Buffon, who noted from Montbeillard's data that stature tends to decrease during the day's activities but that this loss was regained during rest. He also remarked on the existence of seasonal variation in growth rate. Sometimes we think of these as observations of much more modern times. I must not linger too long in the 18th century. My purpose in mentioning Montbeillard and Buffon is to point out, in all humility, that what we are attempting in the middle of the 20th century does not represent a new concept, however modern some of our techniques may be.

Concern with the child as a person in the process of becoming an adult was already a very ancient and honorable human interest when Montbeillard started measuring his son. For example, the Babylonians in 2000 B. C. gave thought to this same problem. I am again indebted to Richard Scammon for a translation of a bit of an old papyrus in which the state's responsibility for illegiti-

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*Special article.

mate children was discussed. The opinion was expressed that existing knowledge failed to show any evidence that such children could not develop into just as good citizens as legitimate children. The statement was then added that there was need for a great deal more knowledge about how a child could be helped to develop into the most useful citizen.

I may mention one other example of the antiquity of this interest of people in the development of their children. Some of you will remember the delightful little bits of "Pediatrics of the Past" which John Ruhrah used to publish in the *American Journal of Diseases of Children*. One such excerpt depicted the concern of the rulers of the Egyptian dynasty in 1365 B. C., for the development of their daughters. Actually it is not very difficult to pick up evidences of similar interest in many lands among many races during the past 20 centuries.

When physicians think of the advances of the 19th century they are apt to concentrate on such contributions as those of Virchow to cellular pathology or of Claude Bernard to physiology and experimental medicine. I have, of course, no intention of belittling the brilliant advances in the medical sciences made by men like Bernard, Pasteur, Virchow, and other giants of that century. I would, however, like to call your attention to the contributions of such men as Quetelet, Darwin, Galton, or Freud as being of equal importance for the pediatrician of today. Quetelet's thesis entitled "Sur L'Homme" in 1836, and his statistical handling of individual variation, foreshadowed much of our present approach to the study of human growth. By the end of the 19th century that beloved British physician, Sir James Mackenzie, had expressed, as well as any physician has, the concepts which motivate the study of the human life cycle today. At about the same time, Freud had raised the most fundamental questions about the early phases of the development of the individual's personality.

At this point it will be well to remind ourselves that novelists, poets, and philosophers have also shown keen awareness of the uniqueness and the wholeness of a person. The stages in the development of Man have been repeatedly described in the literature of many races, long before Shakespeare's description of the seven ages of man. Recently I have been rereading that stimulating book "Man on his Nature," by the great British physiologist Sherrington. I was charmed to note a quotation from Walt Whitman which seemed to express the poet's awareness that we are, each of us, the sum total of all our transactions of living.

> The early lilies become part of this child,
> And grass, and white and red morning glories, and white and red clover, and the song of the phoebe bird,
> And the fish suspending themselves so curiously below there—and the beautiful curious liquid,
> And the water plants with their graceful flat heads—all become part of him.

Thus we see that interest in how each of us became a particular sort of adult is very probably as old as is the record of human thought. We realize also that the concept of carefully following the growth of an individual human being, as a means of gaining more understanding, is far from new. But our 20th century has brought astonishingly rapid advances in our knowledge in all the sciences basic to medicine. These have made it possible to visualize more clearly a future science of Man—to think of medical knowledge as the science of human biology. Whether one looks at the field of biology or physiology, at biochemistry or biophysics, one sees not only tremendous increases in available techniques for studying the development of a person but equally strong reenforcement for the fascination of investigating individual metabolic phenomena. The study of the genes in single-celled organisms, the enzyme systems, the synthesis of proteins, the effect of environmental factors on the living cell, and a host of other investigations now in progress serve to stress the rewarding nature of the study of developing organisms.

Moreover, the clear thinkers in all these disciplines are becoming increasingly aware of the truth of a statement made over a quarter of a century ago by that thoughtful biologist Frank Lillie. He remarked that any biological organism is its own life history, complete from gametes on. This implies correctly that the nature of any organism, at any age or stage in its life, is to be understood most adequately by a study of how it reached that stage. Perhaps an easily understood restatement for the physician would be that the more he understands of the past history of a given person —that is, of the dynamic process of his growing, developing, and adapting—the better he will be able to evaluate the person's present status.

Such considerations are of obvious importance in the diagnosis and treatment of patients in the practice of curative medicine. If one is interested in future advances in the prevention of disease and misery in the world, then they become exciting concepts. Let us take, for example, adult susceptibility to atherosclerosis or coronary disease. If the necessary conditions are laid down during childhood with its active developmental changes, including adaptations to specific foods ingested or to other environmental factors, then we must learn what these conditions are in order to work out adequate preventive measures. There may, of course, be deviant metabolic pathways dependent upon genetic or enzymatic defects. But even so, the possibility would exist for making up the deficient enzyme, or what not, during the earliest years of life, thus avoiding some of the catastrophes of middle life.

Let us take another example, of quite a different sort. I am sure you will all agree that some of our most serious social problems today are in the realm of so-called mental health. The evidence in regard to the frequency of psychological and psychosomatic disorders is so overwhelming as to need no further documentation here. Meanwhile, reliable research is revealing more and more evidence that there are close relationships between life experiences in infancy or childhood and the adequacy of the adult's sound adaptation to his world. It seems probable that we shall not greatly reduce the incidence of severe emotional problems in the adult until we learn what experiences in early life are necessary or sufficient forerunners of the poorly integrated or disturbed adult.

Thus, ultimate prevention of much of the sickness and misery in our adult population becomes a responsibility of those of us who deal with infants and children. Unfortunately, we need much more knowledge and wisdom than we possess today. It is this need which motivates many of the interesting studies in progress today in many parts of the world. The Child Research Council of Denver is similarly motivated. As an institute for the study of the human life cycle, its primary purpose is to increase our knowledge and wisdom concerning how a given child becomes the kind of an adult he turns out to be, physically, physiologically, and psychologically.

When I joined the institute, in 1930, we did not visualize our purpose so clearly. To be sure, we knew we wanted to follow a succession of individual children as each one grew, developed, adapted, and matured from birth through infancy, childhood, and adolescence. At first, we limited ourselves largely to simple measurements of growth in size, combined with observations whose main purpose was the discovery of disease or the evaluation of the healthiness of the child. During the early years—in fact until 1940—much of our time was absorbed in a search for greater wisdom not about a child but about how to study a child in the process of becoming an adult. We owe a sizeable debt of gratitude to many scientists, as well as thinkers in many disciplines, for generous giving of their time and their wisdom. During these years I visited many of the research centers in this country. An account of one episode may serve to illustrate the interest and thoughtfulness of the many scientists who were so helpful to us.

I had written for an appointment with the late A. J. Carlson, who was then still active in the department of physiology of the University of Chicago. He had kindly agreed to give me an hour. When I arrived I told him briefly about our institute, after which I said, "If you were to join our staff, knowing you could keep on seeing the same person year after year from early infancy through childhood into the mature years of middle life, what would you want to observe or measure or test?" That grand old man of science had only just got well started on his answer by the end of the hour. We spent half the morning, most of the afternoon, and half the night completing our stimulating discussion. Much wisdom and exciting stimulus came from each of dozens of such conversations with many persons, representing many fields of knowledge. Not only did our ultimate goal become clearer, but the means for reaching it began to take shape. Meanwhile, our affiliation with the University of Colorado was becoming closer and of greater mutual benefit, so that, in 1946, the regents asked us to serve as the Department for the Study of Human Growth. During these past 10 years the general philosophy and organization of the program have remained reasonably constant.

By now our over-all theoretical concept should be clear. We believe that each of us, as a biological organism, is built as he is, functions as he does physiologically or biochemically, and behaves as he does emotionally as a result of all that has gone before in his life. This involves the original genetic endowment bestowed at the moment of conception plus all the transactions between this original tiny fertilized ovum and its environment as it develops into a complex multicelled human organism. We also believe that by following such an organism as a person, from birth on, as carefully and continuously as is feasible, we may be able to sort out some of the multiple factors which lead to the individual person's particular strengths and weaknesses, physically and physiologically, health-wise or personality-wise. And, finally, we believe that a person is an indivisible biologic unit—that the impact of some environmental stimulus at one level of organization most frequently produces changes at more than one level of the organism's functioning. It follows that if one is to learn more about the effect of life experiences on a growing person one must attempt to observe many structural and functional aspects in one and the same person over the same time period.

This last point seems to me like a rather simple logical sort of idea. However, it is apparent that in both clinical and research activities it is often either not accepted or not appreciated. At any rate, it is fundamental in the planning of our program of research as well as in the organization of the staff. On the one hand, it has led us to sample various aspects of structure and function of each subject at regular intervals, as, for example, changing size and proportion of different parts of the body; the changing food intake and nutritional status; adequacy and constancy of physiological adaptations as reflected, for instance, in cardiac and respiratory response to stress; the individual's characteristic levels of the globulins in the serum or of the blood cells, compared with his responses to infections; the earliest evidences and subsequent changes of emotional responses to life's experiences as we watch the development of personality characteristics, and, of course, a continuing interest in evaluating over-all healthiness during growth.

On the other hand, the concept of a person's indivisibility had led us to favor a research staff whose members are primarily interested in what their special knowledge and skills, drawn from specific fields of science, can contribute to the understanding of a person. Although the families of some of our 188 subjects sometimes refer humorously to their children or themselves as "our guinea pigs," there is a general awareness that we are not using human subjects primarily as a means for gaining knowledge for a particular field of science. Rather,

we are using all the sciences basic to human biology and medicine as tools for gaining new knowledge about a person. This is more than just a play on words. It is an important aspect of our approach to the study of individual human life cycles. It leads to a community of interests among staff members from different scientific disciplines. This makes cooperative ventures between them the rule rather than the exception. I do not mean to imply a Utopian or unrealistic situation. We have, justifiably, some investigators who are more narrowly concerned with their own fields than others. I do mean to imply an unusual degree of cooperative effort which cuts across two or more disciplines.

I have spent a good deal of time on the general concepts and the whole philosophy which underlies our program of research. It must be apparent that in the detailed carrying out of the program we consider many theories or hypotheses or, it may be, just intelligent speculations. These serve to orient or to help in the designing of our studies in the hope that we may validate, invalidate, or elaborate theories and ideas in various fields of human development. I shall return to some of these tomorrow evening. For the remainder of my time tonight I shall outline our current program of research.

We are now following 188 subjects, drawn largely from the middle socioeconomic groups in Denver's population. Their ages vary from two not yet born to 20 young adults in the age period from 25 to 30 years. We have enrolled only 5 to 8 new babies a year, so that in each five-year age period there are 30 to 35 subjects. Twenty of those under 10 years are "second-generation babies" in the sense that one parent has been followed since birth in the Child Research Council. Most of the subjects added in the last five years are either new siblings born into families already being followed or else second-generation babies. We are still following 80% of all subjects enrolled since September, 1930.

The study of each new subject starts with the family before the end of the first trimester of the pregnancy. Thus we are able to obtain some understanding of the father and mother, and of the home into which the baby will be introduced, well before the baby is born. Our chief interests in this prenatal period have included the mother's health; her dietary intake, food habits, and nutritional status; the course of her pregnancy; the social setting of the family in the community, and the personalities of the parents. In the whole sociopsychological area we are greatly interested in attitudes toward child rearing and in what one might call the parents' pipe dreams about the coming child and his future. The family and home are visited at least once a month and frequently more often.

One of the most valuable aspects of the prenatal visits by staff members is the opportunity it affords for orienting the parents in regard to the part they can play in our total research effort. They usually become aware of the variety of our interests, at the same time gaining some insight into the vast areas of our ignorance and why we are excited about exploring these areas. Most of them also have time to become comfortable with our lack of willingness to become involved in therapeutic problems. They learn, too, to appreciate our willingness to refer them to their physician and to keep in contact with him when necessary. Throughout the following of each subject routine reports on health and progress go, ordinarily, to both physician and parents.

From birth on, every member of the staff is involved in some way with each subject. On the day of birth a team of investigators visits the hospital where the baby happens to be born. Complete examination, measurements, and prolonged observations of the baby and interviews with the mother form the start of this new person's life-long follow-up. The clearest way of describing the various observations made on each of our subjects is to outline them under the general headings of physical growth, phys-

iological development, and personality development. Actually, there is no such sharp division of responsibility nor is our staff divided into departments. For, such procedures as determining the basal metabolic rate in a closed chamber, doing a venipuncture, or making a home visit to check on food intake may yield useful knowledge or insight into the psychological nature of a child. And it is equally true that the psychologist, either in a home interview or in a set play session in our observation room, may discover information of value to physiologist, nutritionist, or pediatrician. Thus the division of our activities into three categories is a somewhat arbitrary division.

Physical Growth

We think of the study of physical growth as an investigation of the patterns of change in the various structures of the body during growth and maturation. Perhaps because anatomy for most of us seemed like such a static subject, we tend to forget that the child's structures are constantly changing. We are interested less in the measurements at any one age or stage of development than we are in how they reveal the changes in different structures during growth from one age to the next. Ultimately, of course, we are searching for the significance to the individual, in his future adaptations, of his own pattern of growth and maturation.

To reveal these patterns for each child we make use of (1) direct measurements and observations of the child, (2) photographs, (3) x-rays, and (4) mathematics, statistics, and graphs. The investigators most intimately involved in this area of study are Dr. Jean Deming, Dr. Marion Maresh, Dr. Edith Boyd, and Dr. Frank McFeely. The first three are physicians whose combined experience ranges over such diverse fields as pediatrics, roentgenology, anatomy, internal medicine, hematology, biometry, and general practice. Dr. McFeely is a biostatistician who works with all members of the staff. Dr. Boyd makes use largely of direct measurements and photographs, being absorbed in the pursuit of a better understanding of external body proportions. Dr. Maresh utilizes chiefly x-rays of head, chest, spine, hand, foot, and long bones. Developmental patterns of the respiratory tract, the heart, and the bony skeleton have been her chief interests. Dr. Deming spends her major effort on the detailed analysis of individuals' patterns of growth in height, weight, and certain other dimensions. Dr. Deming also takes her turn, with three other pediatricians on the staff, in examining the children.

I should like to show a few slides,† taken from the work of these investigators. These may serve to illustrate our approach to the study of varying patterns of growth in different persons. In Part II, I have more to say about individual variation and its possible biological and clinical significance. Now, I shall be content if you note the broad range of variation within the human pattern of growth, together with the tendency toward consistency in the patterns of any one person over a time period.

Physiological Development

To study the changing physiological functioning of all aspects of any one person throughout his life would represent a very large order. It must be obvious that in any one institute, like the Child Research Council, we can undertake only arbitrarily chosen samples of the child's functioning. So far, our sampling has included (1) the appraisal of over-all health as well as of the presence or absence of specific diseases; (2) the study of heart and circulatory functioning clinically and by means of x-rays, electrocardiograms, bicycle ergometer tests, vital capacity, and maximum ventilatory capacity; (3) nutritional appraisal by careful record of food intake (home visit); the levels of cells, hemoglobin, proteins, cholesterol, vitamins, and alkaline phosphatase in the blood; basal metabolism determinations and O_2 consumption in nonbasal states, and the

† The illustrations shown at the lecture were taken from References 1 to 6.

previously mentioned assessments of physical growth; (4) observations on resistance and long-time response to infections by means of clinical observations, x-rays, blood cell studies, and the electrophoretic and chromatographic study of the protein fractions; (5) simple tests of motor function, coordination, strength, and speed of reaction with and without decision-making; (6) the flicker-fusion test, and (7) electroencephalographic studies on both parents and children. This group of investigations involves the largest group of staff members, headed by the Associate Director, Dr. Robert McCammon, and including Drs. Iliff, Trevorrow, Meyers, Lee, Metcalf, Sexton, Deming, and McFeely and Miss Beal, Mrs. Root, Miss McKean, and the Director. The education and experiential backgrounds of this group are impressively varied, as is the case with those in the physical growth field. There are four with M.D. degrees and six with Ph.D. degrees.

Without going into the details of all the observations or determinations made by these investigators, I should like to point out several pertinent aspects of their work. This is the group par excellence which stimulates cross fertilization of thought process between all the disciplines represented on the staff. It is also the group which takes the most active part in true multidisciplinary ventures. For example, pediatrician, protein chemist, and hematologist are investigating the individual variations in handling infections, or a physiologist and biochemist work with the head of the metabolism unit studying O_2 consumption under varying situations of stress, or, again, physiologist, pediatrician, and psychiatrist are absorbed in the interpretation of electroencephalograms in relation to the child's behavior and other characteristics. Furthermore, these staff members all have continuing direct contact with the children whose development we are following.

Personality Development

Personality development represents our third general area of investigations. Here we search for the answers to many questions concerned with understanding the multiple factors which combine to create the adult's own unique personality. How much can we say about what sort of a person this baby is at birth? What are the significant early experiences through which, bit by bit, he learns his own concepts of the world in which he lives? How is this new immature person reacting week by week to the experiences of the early months or years, and what effect do such reactions have on subsequent patterns of behavior? What preschool-age anxieties does he reveal, and how does he handle them? What sort of picture of himself and his place in the world does he have as he starts grade school? And how well do these responses foreshadow the degree of stability in adolescence or the sort of adaptation he shows as a young adult?

Dr. John Benjamin leads a close-knit team including Dr. Henry Ricciuti, Mrs. Tennes, and Mrs. Randall, pursuing the answers to these and many other questions. In infancy prolonged and frequent observations are oriented toward the early characterization of the baby as a person with certain traits already observable and testable. Infant testing follows fairly closely the pattern of the Hetzer-Wolf tests as performed by Dr. Katherine Wolf, at Yale. Through the preschool years we make use of such projective techniques as doll play, painting, clay modeling, free play, thematic apperception test, Rorschach test, the Wechsler-Bellevue or Stanford-Binet test, and a variety of interviews. Into and beyond the grade-school years, while we continue routine testing at less frequent intervals, we become increasingly dependent upon a variety of interview techniques. Periodic home visits add valuable insights, as do, of course, regular interviews with the parents. When all these observations are combined with reports from pediatrician, nutritionist, and others on the

staff there results a large volume of information on the development of a given child's own personality in his own environment.

The theories of personality development, derived from the pioneering work of Freud or of those in psychology who have continued to apply a dynamic approach to the study of personality development, lend themselves excitingly to our particular program. One can hardly imagine a better setting in which to validate or invalidate such concepts. Moreover, there is every opportunity to elaborate current too-narrowly-conceived theories by the utilization of social, cultural, and biological data on these same children whose total study in the Child Research Council samples so many areas of structure and function.

This completes what I want to say about the philosophy and program of our research. I trust it will serve as adequate background for what I want to say in Part II. I shall attempt to trace a picture of the expected pattern of development and adaptations during an individual person's growth, in the light of our studies to date. I have given Part II the title "More Questions Raised Than Answered" because at the present stage of our investigations we have neither a lot of "pat answers" nor any grand conclusions. In spite of this, I hope I may be able to hand on to you something of the enthusiasm of the members of our staff as they pursue their investigations.

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The Child as a Person Developing*

II. More Questions Raised Than Answered

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In Part I of this paper I presented some of my thoughts about the study of human growth. I should like to restate, in simple outline fashion, the steps in my thinking about the physician's need for a better understanding of growth.

1. The physician is faced with a person as a patient—an individual human being, not abstract Man.

2. Any such person is an indivisible biologic unit.

3. Such a living organism consists of its whole life cycle, from gametes on. That is, the organism is as it is at any age or stage of its development because of what has gone before.

4. What has gone before includes, first, a unique inheritance from the genes; second, the nongenetic inheritance of cultural habits and codes of behavior, and, third, an individually unique series of interactions between this new developing organism and its environment. John Dewey's term "transactions of living" suggests the nature of these experiences through which the infant and child attempts to adapt himself to the demands of his society or the exigencies of his environment.

5. Many of these experiences in early life play a significant part in determining both physiological and psychological functioning in later life.

6. Variations between individuals, present in every aspect of structure and functioning, carry great significance in diagnosis and treatment as well as presenting a challenge to biological and medical research.

7. Adequate study and evaluation of a given person's past history, and present observed status, necessitate certain basic knowledge and understanding of the nature of a person as well as of the diseases from which he may suffer. This should include knowledge of (*a*) the general human patterns of progress to be expected as a person develops physically, physiologically and psychologically, at least from birth if not from conception; (*b*) the general nature of the human mechanisms of adaptation and defense, including patterns of breakdown of these mechanisms leading to maladaptation of disease; (*c*) the significance of individual variation—of the more common deviations from the average and of how to evaluate them meaningfully in the diagnosis, treatment, and prognosis of a particular person.

I shall devote the major share of this paper to the three last-mentioned topics. The general human pattern of growth is well known. The expected human patterns of physiological, biochemical, or biophysical responses to environmental stimuli are not so well established. However, knowledge in these areas is increasing by leaps and bounds in this 20th century—so rapidly, in fact, that it has become difficult to keep up with the progress in so many fields. In the area of psychology and psychiatry there are also rapid advances. These involve not only increasing understanding of the mechanisms of adaptation of a person to his cultural milieu and other environmental factors but also increasing insight into the way in which an individual personality develops through such experiences.

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* Special article.

In contrast to these advances is the slow progress made in the investigation of individual differences, particularly in regard to their specific significance for the health and soundness of a person through the life cycle. I shall attempt to describe some of the things we know and some of the things we would like to know in this area. In order to do this in orderly fashion, I shall follow the expected human pattern of progress from birth through childhood and adolescence, much as we have been doing on each subject in the Child Research Council for many years. As was the case in Part I, I shall continue to consider the child as a person going through the dynamic process of becoming an adult. Since the problem of individual variation is constantly present through all age levels, it may be well to make a few general comments about variation before tracing the pattern of growth.

Rorschach once remarked that if one could find a "normal" person he would turn out to be such a rarity that one could not justifiably call him "normal." Certain it is that the range of variation found in most of the structures and functions of children is very broad during what is apparently healthy growth. The range from minimum to maximum in some measurements represents a threefold to fivefold increase. If one divides such a range into percentiles, plotting the individual person's curves against the curve of the percentiles, it soon becomes apparent that it is meaningless to call any one percentile level, such as the 50th or the 90th, "normal." Three equally healthy persons may be short (10th), medium (50th), or tall (90th percentile). Actually, the situation is much more complex and more fascinating than is indicated by this simple example of variation in height. For example, there is an obvious difference, which is concerned with health, between two children one of whose γ-globulin level is persistently at the 90th while the other's γ-globulin level is just as persistently at the 10th percentile. To suggest still further complexity, I might mention two boys who are different in many ways. The observations on the first show height at the 50th and weight at the 95th, with blood pressure at the 98th and cholesterol at the 90th, percentiles. He also shows some unusual proportions, giving him a top-heavy appearance, and his efficiency on the bicycle ergometer places him at the 25th percentile. The second boy reveals a height at the 95th, weight at the 35th, blood pressure at the 50th, cholesterol at the 30th, and bicycle test results at the 75th percentile. Both are now young adults; both were described as showing healthy growth, and each has been called "normal healthy young adult." Surely they are very different, and just as surely they face quite different hazards in middle life. To apply the term normal is worse than meaningless, since it blinds us to their differences, which should be our chief concern in trying to help each one to live a long, happy, useful life.

Early in our investigations we were impressed with the dangers inherent in failure to recognize the existence of wide individual variations. One of our best illustrations was in the hematological field. We could show a child whose usual erythrocyte sedimentation rate (ESR) was so slow that it was seldom above our 10th percentile. When she had an acute otitis the curve showed a sharp peak, but the range of variation in sedimentation rates is so great that even at the peak of increased rate her curve barely reached our 90th percentile. We had another child whose usual rate was at our 90th percentile. A doctor seeing her during a minor illness, with vague aches and pains, made an erroneous diagnosis of rheumatic fever on the basis of what he considered a rapid ESR. We have had many similar illustrations revealing the need to know the possible amount of variation in order to diagnose and treat children safely.†

We are, of course, still concerned with stressing this aspect of individual variation. In recent years, however, we have become fascinated by some much more significant

† Slides were shown illustrating some of these points. These were taken from References 1, 2, and 3.

and fundamental questions about variations. Why are there such great differences in structures and functions? Is this entirely a genetic problem, or are there environmental factors involved? What does it mean for his future health if a particular child has a particular biochemical or physiological finding deviant from the average for the group? And, finally, if some of these deviant characteristics reflect potential weakness in future adaptation to environmental hazards, what can be done to correct them, whether they represent genetic deficiencies or environmental handicaps or a combination of the two? A very stimulating book on this subject has just recently been published. The title is "Biochemical Individuality," and the author is the well-known biochemist Roger Williams, of the University of Texas. I hope his recent election to the presidency of the American Chemical Society may serve to give his thought-provoking book wide circulation.

I have taken the time to stress the significance of variation between persons because it has such tremendous importance in both clinical and laboratory diagnosis. I suspect it will have increasing importance in future research in human biology. In the following account of the human pattern of development such variation is constantly implied, whether mentioned or not.

I shall not attempt to cover development from conception to birth. Here in Cincinnati, the home of Dr. Warkany, I hardly need to point out that the most hazardous period in the baby's prenatal development is in the first three months. This is the period when dietary deficiencies or diseases in the mother are most apt to produce defects. In spite of many unanswered questions, we do know that it is important to educate people to realize the importance of diet and health for the prospective mother in the months before conception, as well as during the early weeks of the pregnancy.

As any one knows who has observed thoughtfully many babies during the newborn period, they are already different persons at birth. Each newborn baby presents already some very definite unique characteristics of his own as well as his own biological potentials derived from his parents and perhaps already distorted by his environment in utero. I state this rather trite fact because it seems to me that in the feeding and care of small babies—particularly in institutions, but to too large an extent in practice also—we act sometimes as though this were not so. The current fad of very early addition of solid foods to the diet illustrates this nicely.

In terms of understanding the coming interactions between baby and mother, it pays to attempt some evaluation of the baby as early in life as possible. And by "evaluation" I imply more than the routine "physical examination." Incidentally, let me say right here that I wish we could drop the word "physical" from that time-worn phrase "physical examination." Surely in this day and generation we are interested in both soma and psyche. For my part, I do not see how one can justifiably say that one is concerned with understanding the child as a living organism without at least attempting to observe over-all functioning. For example, in examining the baby in the early weeks of life one should be interested in observing such items as motions, whether whole body responses or isolated movements; the use he makes or attempts to make of his eyes; his sensitivity to sounds, that is, whether he seems to use his hearing as a more sensitive instrument and to respond more readily to voice, to pleasant sounds, or to harsh sounds; his reaction to touch—whether it quiets or disturbs him—whether he likes being held or whether it makes him fuss, etc.; his alertness, his degree of quiet relaxation as against hypertonicity; whether he is essentially peaceful or dynamic; his degree of oral drive both in the nursing situation and in periods of either hunger or satiation; his degree of independence versus his apparent need for support and comfort. One should have in mind the question, "How will this baby's characteristics react on the mother?" to produce either a particular hazard or a particular advantage to

the baby—somatic as well as emotional, since the two are so inseparable.

To attempt to say what sort of a person the newborn baby is, or is in the process of becoming, is a vastly more difficult task than to assure oneself that heart and lungs are healthy. And yet, if we are correct in assuming the importance to his future happiness of the nature of his reactions and learning in the early years, may not such an evaluation be of as much or greater importance?

During the first year of life it is apparent that many of the problems for which the mother seeks pediatric advice are the result of interactions going on between this particular mother and her particular baby or between the baby and other aspects of the family's life. Is it not probable that many instances of mild diarrhea, constipation, spitting up, colic, rashes, and so-called feeding problems belong in this category? They may be dependent not upon one but upon multiple factors, which include this particular baby's physiological and emotional characteristics as they interact with the emotional and personality traits of those handling him. To straighten out such problems in a way as to promote this baby's future strength and balanced adaptation to life requires a sound evaluation of the causal factors involved before changing feedings or giving medication. Probably no characteristic of the physician is so valuable to him and to the patient as fascinated curiosity about the unfolding pattern of the personality of a human being in the first five to six years of life. To be sure, he needs medical knowledge and skill as well as tolerant sympathy for mother and baby. This latter will follow naturally if he is really absorbed in trying to understand the development of a human being. It can be more fun than unraveling the plot of a detective story.

I do not mean to imply that interpretation is a simple matter—quite the contrary! That is why it presents a good challenge. It is complicated by the physician's own personality characteristics, into the nature of which he may or may not have good insight. For example, he may be so constituted that he has more sympathy with the mother than with the baby when the mother complains that the baby is constipated. Or, in another instance, when the mother is disturbed over the baby's spitting up, the physician may be annoyed with the mother and belittle the symptom in the baby without further analysis of the situation. In other words it may be the physician's own problems—and we all have them—which make it difficult for him to imagine that such symptoms as spitting up and diarrhea may represent rejection, or that constipation may reflect tightness and withholding. As another example, is it not possible that strong oral drives in a baby whose mother has either never had them or has repressed them as "bad" may lead to feeding problems and later to excessive thumb-sucking? We are all familiar, too, with the greater incidence of "colic" in the presence of tensions in the family—particularly, but not necessarily, in the mother. I remember a young physician who was sure, before his first baby was born, that there was no such entity as "colic"—it was all in the imagination of a "high-strung mother." A few weeks after his first baby was born he came in to see me, admitting gloomily that his baby had "colic." He himself was a very tense person; his wife, relaxed. It was hard for him to accept the situation, but he did much better with his subsequent children.

The majority of babies in averagely healthy American homes grow rapidly and smoothly through the first 6 to 12 months of life, with a minimum of illness. So often one sees an epidemic of colds in the family but baby only had a bit of sniffles for a few days, not even appearing sick. The infant's growth follows a smooth exponential curve of steady deceleration which aims toward an asymptote which is essentially a straight line slanting upwards in the preschool and early school years. The average curve of the boys bends more sharply than that for the girls. The boy with the more slowly decelerating curve, similar to that of the girls,

is apt to have more than average gynic components in his physique.[4,5] It seems to take a fairly major catastrophe in the way of severe food deficiency or major illness to prevent the individual baby from following his own ordained pathway. Does this imply hormonal control of andric and gynic characteristics in the first year of life?

In contrast to this usually smooth course of physical growth is the course of personality development. The average baby in our urban American culture is having a much rougher time learning what kind of a world he lives in—struggling to acquire his first sense of himself as an entity separate from his mother. There are so many things to learn. A simple example may be seen as one watches the bottle-fed baby learn that when he cries because he is hungry the mother goes to get food for him. Does the baby keep on crying until the nipple hits his mouth, or does he learn quickly by sounds or sights or touch that food is coming soon? If the latter, he may lie quietly, or even with cooing, until the food arrives, although it takes some minutes. We should be curious as to when and how he acquires faith in the reliability of his world. And what about the future of those babies who, for one reason or another, do not acquire such trust in the early years?

The insights gained in understanding how a given culture strives to preserve itself through its child-rearing practices is invaluable in pediatric practice. One understands the difficulties for the baby born in 1956 in Cincinnati. He has much the same biological attributes as a baby born here 100 years ago or born today in some less sophisticated culture. But what are we asking him to do in the way of conforming to our world of today? And how sure are we that we know what sort of adaptations he should make for the world in which he is to live during the next 75 years? These are sobering questions, which deserve as much historical background as we can acquire, before being answered. Many parents are confused and need sympathetic help in this area. Watching children become adults gives the physician helpful clues as to what is or is not important in rearing the child to take his place in the adult world with sound and healthy adaptation.

As he goes from almost complete dependence upon others into the relative independence of the 1- to 2-year-old is he constantly thwarted in developing his own sense of self and that self's position of love in the family? Or does his environment permit or even encourage the maximum freedom of development of his own potentialities for strength as an independent biological organism within his social environment? These problems take us into the often stormy, so-called negativistic, era of 12 to 24 months. Now the rate of physical growth has slowed to a walk, compared with that of the first five to six months. But his need to assert his self grows by leaps and bounds. He has become the young explorer, striving to discover everything he can about the world around him. This still consists mostly in family and home but with increasing excursions into the world outside. And let us not forget that the physician is a part of this world.

Now increasingly are staged the battles over toilet training, eating habits, dressing and undressing, going to bed or to sleep, touching or breaking things not meant for him to play with, etc. And here, too, is the start of the increased frequency of common respiratory infections, of gastrointestinal upsets, of the exanthemata—in short, of apparent increased susceptibility to many infections. Is this dependent upon increased exposure or is that only one and probably not the most important factor?

It has surprised me to observe how many pediatricians, called upon to care for a sick child in the early preschool years, will treat only the specific obvious symptom of disease. It is as though they made no real effort to make a complete diagnosis and hence failed to take into account many of the possible multiple factors which are so disturbing to the child and can be so in-

teresting for the physician to study. If I had not observed this failure so often I would feel embarrassed to point out that there are interesting relationships between the so-called physical illnesses such as gastrointestinal upsets, diarrhea, constipation, anorexia, or the "common cold" and the developmental stage through which the child is growing. It does not seem like good medical practice to diagnose correctly only the superficial manifestation of disease while neglecting all the rest of the biological organism. If the child as a developing person is to be helped to grow into a healthy, independent, well-balanced, secure person, then the dramatic 'cure" of his symptoms with drastic changes in his food or with laxatives, antibiotics, or other medications may, in a given instance, be quite contraindicated.

We are at present engaged in a careful analysis of the frequency and speed of recovery from upper respiratory infections in our children with and without antibiotic therapy. We are also noting their lymph node response and their blood proteins and cells. I regret that I am not able to give a final answer in our group of subjects. However, it seems possible that we may have to ask the question why those without antibiotic therapy show the more favorable records. Certainly what many children need—and their parents also—is faith in their own natural ability to adapt to their environment in a healthy manner.

At this point I should like to call your attention to a delightful article by E. B. White in *The New Yorker*, June 30, 1956. It really should be "must reading" for young physicians and scientists. I shall take the liberty of quoting one sentence which is apropos of the point I have been trying to establish. "I would feel more optimistic about a bright future for man if he spent less time proving he can outwit Nature and more time tasting her sweetness and respecting her seniority."

Both children and their parents need something of E. B. White's "respect for the sweetness and seniority of nature"—their own nature too! I do not mean to sound nihilistic about drugs—especially those life-saving chemotherapeutic agents which have saved so many lives in so many children with potentially lethal diseases. Nor would I belittle the contribution the physician can make in helping the patient over the rough spots with or without needed medication. But is it not true that the vast majority of the illnesses one encounters in private practice with preschool children are to be classified by a word little used today, namely, "self-limited"? They will clear up in time if we do not do anything to hinder the patient's recovery.

Let us remember also that the majority of these illnesses and problems in the childhood years have not just one simple causative factor, such as a particular micro-organism. Rather, they are caused by multiple and often complex factors—physical, biochemical, psychological, and social—some concerned with inherent characteristics of the person and some with the environment. With the rapid multiplication of antibiotics, together with the ease of relieving alarming symptoms by their administration, the young physician is in danger of forgetting the challenge of really establishing an adequate diagnosis. He is in danger of losing the very genuine satisfaction of really knowing thoroughly the courses of events which lead up to the illness, the effect of the illness on this particular child, and how the illness has influenced eventually the multiple causative or contributing factors. Lacking such understanding, the physician fails to treat the human organism—he merely kills some micro-organisms, which may have been only a minor causal factor, like the match that lit the bonfire which was already built and soaked with kerosene. The child is then left prey to other harmful environmental factors, often without having the advantage of learning through experience anything about his own powers of adapting to environmental handicaps.

I mention these problems in relation to my discussion of the preschool era because this is the period par excellence when the

individual child as a person is wrestling mightily with many puzzles or anxieties. He struggles with the concept of self, with the control of the primitive urges of that self, with his relations to father or mother or siblings. Then come the endless parental commands of "do" or "don't." He strives to internalize his authority so as to be independent, and so we have the developing superego or conscience to balance against the ego. Thus he really struggles with the problem of his own integrity, of confidence in himself as a person who will one day be a man or a woman living self-sufficiently in the world as an adult citizen of his community.

Evidence increases steadily that these preschool years are most critical in establishing the foundations for a sound viewpoint about one's place in the world. Should we not, therefore, give more thought to what the child is experiencing at the time we are called to treat illness? And should we not give particularly careful thought to both diagnostic and therapeutic measures, lest we do more harm than good to the ultimate development of this person?

From the more stormy preschool years most children advance into relatively quiescent school years up to adolescence. I do not mean to imply that school children may not be noisy but rather that both growth and behavior conform to a more orderly and socially acceptable pattern. Most growth progresses more nearly in a straight line than before or after. Each child tends to hold consistently to his own percentile zone, whether in bone growth, basal metabolic rate, or physiological functional tests. The grade-school child is developing socially more rapidly than in any other way. Most of the acute anxieties of the preschool years become relatively dormant—hence the psychological term "latent" applied to this period. Finger pricks, venipunctures, injections, or accidents are more apt to be taken in their stride, though there are, of course, interesting exceptions which deserve study. Learning is rapid, while teacher and the gang begin to compete with family as authorities about the world or about codes of behavior.

Infections, particularly of the upper respiratory passages, continue to be frequent but with great individual variations, from 0 or 1 to 10 or 12 in a year. This is a period of slowly increasing resistance to, and quicker recovery from, illness in many but not all children. It is a comfortable time to examine all health factors in a leisurely manner, evaluating assets and liabilities for prescribing long-time health practices. The grade-school child is apt to be easier to handle, to understand, and to help than either the preschool child or the adolescent. Hence, if one particular child is not the physician should be interested in trying to ascertain why not. The child's own norm or baseline for various physical and physiological characteristics is well worth establishing in this period.

The start of adolescence I shall somewhat arbitrarily date as the beginning of the growth spurt. This coincides approximately with the first appearance of such secondary sex characteristics as enlarging genitalia, pubic hair, or breast enlargement. Puberty as a point in time has usually been set in girls by the start of the menses. Perhaps a more satisfactory criterion for both sexes would be some such definite point on the height curve as the inflection point when growth shifts from acceleration to deceleration.[4,5]

Any one who has been the parent of an adolescent boy or girl knows full well that adolescence is a difficult period for the child just about to be an adult. The drive for emancipation—for the complete independence which he imagines adults have—is often in sharp conflict with his strong desire to hang on to the love and security within the family circle. The adolescent wants to use the family car but wants it without strings of responsibility attached. He wants to be out late and do what he pleases but wants his own home and bed at the end of the evening. It's really the old conflict of how to have your cake and eat it too.

Fortunately, for most children this period is apt to be relatively free of serious illness. The incidence of infections decreases, often sharply. Accidents really represent the biggest hazard. There are, however, apt to be many minor complaints and somatic worries. Their bodies are closely associated with their emotional turmoil. As in the preschool years, symptoms which bring the adolescent to the doctor are apt to have multiple causal factors which involve physiological, psychological, and sociological problems. Certain items seem worth stressing.

The first point which is of great interest to the physician is the fact that so often the stage is set for a stormy adolescence during the preschool years. Here an ounce of prevention would be worth several pounds of cure. The child with an acutely anxious time at the age of 4 to 6 years, full of unsolved problems about himself as he goes into the latent period of the grade-school years, is very often headed for a stormy adolescence. The boy who has not visualized himself well as a man with wife and family of his own, who is confused about his relation to his mother and wants her for himself, is typical. So, too, the little girl who is jealous of her mother and wants her father to herself may be just as much in danger if she has not straightened out her thinking before going into the latent period. I don't mean to oversimplify. It's not just the problem of the "Oedipus complex," important and common as that is. There are many possible anxieties which need at least some solution satisfying to the 5- to 6-year-old. Otherwise such problems get lost in the unconscious realms of the mind, so that the disturbed adolescent often has very little conscious idea about, or insight into, his own disturbance. I am not asking pediatricians to be psychiatrists or psychotherapeutists. I am asking them to observe, to read, to study, to be skeptical, but yet to be aware of such factors which are of potential significance in the development of each child. With insight comes tolerant understanding, which may be what most adolescents need more than psychiatric care.

The second point I want to stress is the very great difference in the timing of adolescent changes. There are two facets to this situation. Girls, on the average, start their adolescence and progress through it two to three years ahead of boys. Is it not true that in our schools, in many of our social organizations and customs, and even in medical practice we often act as though we did not know this? During the early part of the girls' adolescence they are not only bigger than the average boy of the same chronological age but they are also more mature in both physical and mental traits. Thus mixing boys and girls at this stage, which is approximately at ages 11 to 14 years, leads to predictable stresses and strains.

The other facet of the differences in timing is the existence of extreme variations in the onset and in the duration of adolescence in persons of the same sex. In our own small group the average age of the girls at puberty is about 12½ years, but the range is 9 to 15 years. Similarly, boys, with an average of about 14½ to 15, show a range from 11 to 17 years. An occasional girl and a good many boys continue to show increases in stature beyond 20 to 21 years. A good many of each sex, although, again, more among males, show a continuance of some of the psychological attributes of the adolescent well past 21 years. The anxieties, stresses, and difficulties of the child whose timing of adolescence deviates far either way from the average are fairly obvious. In spite of this, the resulting symptoms are not infrequently blamed on other, less significant, causes.

A third group of potential problems is related to the remarkable changes in physique as the boy becomes a man or the girl a woman. Part of them are, of course, related to the specific sex characteristics. Less directly related to the awareness of sex are the changes in proportions of various bodily segments or parts. The typical male shows

greater relative growth in height than in weight, and in muscle than in other tissues. He becomes broader-shouldered, with great development of the muscles of the arms, back, and shoulders; narrow hips, and lean, obviously well-muscled, legs. The typical female becomes broader-hipped, with relatively greater gain in weight rather than in height. She develops more subcutaneous fat and soft tissues, so that her extremities present smooth soft curves rather than visible muscles. As we know, we are all mixtures of andric and gynic components. Hence we are prepared for the finding of extreme deviations from any theoretically typical masculine or feminine build. There is, however, for the adolescent child a considerable handicap to overcome if he or she deviates too far from the models his culture idealizes as the admired male or female figures. In our current American scene the slender and less gynic girl has an easier time than has the boy whose physique contains obvious gynic components. Some of these boys who tend to mature early, and to be both large and heavy, find compensation in a very masculine sport, holding down a "line" position on a football team. Others do not have sufficient size or stamina for this. Some find other compensations, even competing with the girls in the more aesthetic or artistic school activities. Many, however, who find no compensation, turn up with both physiological and psychological symptoms as the expression of their anxiety.

The fourth consideration is the difficulty of understanding an adolescent—especially if you are seeing him for the first time. Traditionally this difficulty is shared by teachers, parents, and physicians. Both physical and physiological attributes are involved along with the psychological. Their very speed of change is diffcult to accept, so that they themselves often act as though they had not quite accepted its magnitude. Then there are physical changes which may puzzle the physician. We were much interested a few years ago to note how fast the heart increases in size in an adolescent whose growth is showing a big spurt. It may even increase in size so rapidly as to make one suspicious of abnormal hypertrophy. This is, of course, particularly important to remember in dealing with rapidly growing adolescents whose hearts are being watched closely because of a previous attack of rheumatic carditis.

Fatigue and irritability are common in early adolescence. This is often combined with rather vehemently verbalized assurance from the child that he is all right. On our bicycle ergometer a good many girls cannot finish the four-minute ride, which is the standard test, which they have previously completed. Some who had tried, bravely enough, have collapsed during the ride or fainted as they were near the end. But even with some such obvious physical and physiological changes taking place, it is difficult to get them to discuss such problems.

In later adolescence, while they may still confide little in their parents, they do begin to find adults outside the home with whom they can identify. With such sympathetic older friends they can often talk with great benefit. At this point the thoughtful and patient physician may be able to play a valuable role. Incidentally, he may grasp this also as a golden opportunity to add to his own understanding and insights. Many an older adolescent with symptoms of a somatic nature, ranging from headaches to abdominal pain, can be helped tremendously if the physician will play the part of a sympathetic and friendly listener.

As the height growth curve levels off to its adult plateau, childhood is finished—the adolescent is giving way finally to the young adult. At present this is still a new field for us in the Department for the Study of Human Growth. It is a chapter that is not yet written. I feel confident that the next 25 to 30 years will yield data and interpretations of extraordinary interest and value. For by 1985 we shall have followed a significant number of human beings from birth to the age of 40 to 50 years.

In closing I should like to return for a moment to one aspect of the philosophy of

our program of research. It would appear that the world was never more in need of understanding how we may rear children who will become healthy, soundly adapted adult citizens, each able to develop his own innate capacities to the full while living with others in reasonable happiness and peace. In spite of this, there are many powerful influences tending toward conformity, mediocrity, and regimentation—influences which deny individual variation and belittle the importance of an individual human being.

Surely the understanding of our culture, of its social, economic, political and moral codes, is, in the last analysis, dependent upon our understanding of the importance of a person, including ourselves. It dominates idealistic thinking from the teachings of Christ to the political philosophy of Jefferson. The understanding of other cultures, other races, and other people is fundamentally predicated upon our awareness of the potentialities for the development of many individual persons within many environmental settings. I have a strong conviction that there is urgent need for more and better studies of individual human life cycles. I believe that such research will contribute significantly to both clinical medicine and human biology. And I firmly believe that such investigations of the nature of the dynamic process through which the child becomes the adult will enhance the dignity and the freedom of individual men everywhere.

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Progress in Pediatrics

Juvenile Cirrhosis

A Clinicopathologic Study of Twenty-Seven Cases

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The pathogenesis of hepatic cirrhosis has been in dispute since Laennec first wrote his account of the disease in 1819. The many studies made to solve this problem attest to its difficulty. This difficulty of determining pathogenesis has been as great for the juvenile form as it has been for the adult form of the disease. In order to contribute to our knowledge of the pathogenesis and other aspects of juvenile cirrhosis, all cases studied at the Mayo Clinic which had pathologic verification were reviewed and a careful study was made of the clinical and pathologic aspects of the disease. Some of the cases previously studied by Perozzi have been included.

Material and Methods

Cirrhosis is defined as that condition of the liver which fulfills the following criteria: (1) degeneration of hepatic cells, (2) increase in connective tissue, and (3) the presence of nodular regeneration with distortion of the vascular pattern. It is recognized that in the past the diagnosis of hepatic cirrhosis has often been made without sufficient pathologic evidence, for example, when sections of the liver revealed only a periportal fibrosis without any evidence of nodular parenchymal regeneration. Such a condition does not fulfill the pathologic diagnostic criteria that have been set up for this study.

Juvenile cirrhosis is arbitrarily classified as all instances of cirrhosis occurring in children up to but not including the age of 15 years. In all the cases chosen for the present study, the patients were first examined at the clinic at an age of less than 15 years. Furthermore, with one exception, the tissues were removed for histologic examination (either at necropsy or by liver biopsy at laparotomy) at an age within the range already specified. The one exception is the case of a girl who was first examined at the clinic at the age of 14 years and 10 months and on whom necropsy was performed at 15 years and 5 months.

Data on all cases in which a histologic diagnosis of cirrhosis had been made (at necropsy or by wedge biopsy of the liver at laparotomy) in children from 1924 through 1954 were obtained from the Section of Pathologic Anatomy. In some instances, necropsy had been performed elsewhere, and it was necessary to obtain protocol, tissues, and tissue sections from the pathologist who had performed it. Through these means a total of 27 cases of juvenile cirrhosis were collected for this study. Of this number, 8 proved to be cirrhosis on the basis of histologic examination of tissue removed by wedge biopsy, while 19 cases were proved to be cirrhosis on the basis of histologic examination of tissue removed at necropsy.

The complete clinical records, including laboratory data, reports of roentgenologic examinations, surgical reports, hospital records, outpatient records, and follow-up records, were available on all of the cases selected for the present study. Histologic sections, tissues preserved in formalin, necropsy protocols, and photographs were also

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available for study. All sections were stained with hematoxylin and eosin. Elastic-Van Gieson, alcoholic hyalin, and Mallory-Heidenhain stains were used as indicated.

Results

Clinical Aspects.—In this group there were 19 girls and 8 boys. The ages of these patients at the time of their first examination at the clinic varied from 5 months to 14 years and 10 months, with an average age at the time of the initial examination of 9.2 years.

In the families of 8 of our patients there was a total of 11 additional known instances of liver disease; 6 of these 11 were cases of cirrhosis, and 2 of the patients had siblings who also died in childhood with hepatic cirrhosis (these are included in the foregoing total).

In 15 (56%) of the 27 cases the history suggested that the children had had a previous attack of hepatitis.

Duration of Hepatitis.—The diagnosis of acute infectious hepatitis is impossible to prove on the basis of history alone. Yet one may suspect on that basis that a patient has had this disease. Some of these children had had a distinct episode of jaundice months or years prior to the development of cirrhosis. Others had had an episode of jaundice which we interpreted as hepatitis, the symptoms of which were continuous over a long time, with the admission symptoms proved to be due to cirrhosis. Another had not had jaundice but had been exposed to presumed epidemic jaundice. Table 1 briefly details the significant information.

The average age at which the initial episode of hepatitis began was 5.8 years. In determining the duration of this initial episode, it was necessary to differentiate between the cases in which there was a clear-cut fairly asymptomatic period between the episode of presumed hepatitis and the appearance of the signs of cirrhosis and the other cases, in which some, or all, of the symptoms and signs of the presumed initial hepatitis continued until the appearance of the signs of cirrhosis. In the former group, the average initial episode was 2.8 months in duration, while in the two groups taken together this lasted an average of 11.6 months. The difference between cases with and without continuous symptoms of hepatitis affected only slightly the average figure for the interval of time between the onset of the initial episode and the appearance of the signs of cirrhosis. However, the range for this interval of time was wide, extending from 3 months to 12 years, with an average of 3.1 years for all cases.

The histories were not detailed enough to enable us to determine the dietary background of the patients in this study. If any dietary deficiency existed, it was on a basis of choice and not of deprivation due to poor economic status.

Symptoms and Signs.—The frequency of the various symptoms noted in the histories is given in Table 2. Symptoms referable to a preceding attack of presumed hepatitis are omitted, because this phase of the study has already been reviewed in Table 1. In those cases in which some of the symptoms suggestive of hepatitis persisted until the appearance of definite signs of cirrhosis, only those symptoms which persisted beyond the acute episode are retained for the present discussion.

The high frequency of a bleeding tendency (most often manifested as epistaxis) in these children, as distinct from hematemesis and melena, should be noted. Another interesting finding was the high incidence of fever, even though those symptoms (including fever) due to a possible preceding hepatitis are not included in the present figures. Nevertheless, we found that 12 of the patients (44%) had fever.

The appearance of peripheral edema often presaged the appearance of ascites and was therefore of prognostic significance.

Table 3 presents an outline of the clinical findings. Splenomegaly and hepatomegaly were observed in most of the patients. There were a few in whom this association of signs was not found. Thus, four had only an enlargement of the spleen (without ac-

TABLE 1.—*Initial Episode: Cases with History Compatible with Previous Hepatitis*

Case	Age		Duration, First Attack	Interval, First Attack to Cirrhosis	Symptoms, Gastrointestinal Disturbances						Remarks
	First Attack	Admission			Jaundice	Anorexia	Emesis	Abd. Pain	Acholic Stools	Fever	
1	6 yr.	9 yr.	1 yr.	3 yr.	+	0	0	+	0	+	Initial gastrointestinal complaints off and on for 1 yr.
2	3 wk.	4 yr.	7-8 mo.	13 mo.	+	0	0	0	+	0	Jaundice not due to atresia, erythroblastosis, or syphilis
4	13 yr.	14 yr.	See remarks; 1 wk.	5 mo.			No notation			+	After episode of fever, had fatigue, irritability, pallor, menstrual irregularity, all persisting 5 mo., then had hematemesis
5	?	12 yr.	?	?	+	0	0	0	0	0	Long history (duration?) of recurrent jaundice
7	First 5 mo.	6 yr.	5 mo.	5 yr.	+	0	0	0	0	0	"Born with jaundice," which persisted 5 mo.; diarrheal episode, age 13 mo.
9	15 days	13 yr.	4 mo.	12½ yr.	+	0	+	0	0	0	Mother had jaundice, age 17 yr.
10	4 3/5 yr.	11 yr.	Continue 7 yr.	See remarks; 7 yr.	+	0	0	+	+	0	Jaundice fluctuating for 7 yr. previous to admission; abdominal distention and abdominal pains began 3 yr. before admission; enlarged spleen 7 yr. after onset
13	11¾ yr.	12¾ yr.	Continue 14 mo.	14 mo.	+	0	0	0	+	+	Symptoms continued 14 mo., when liver and spleen were found enlarged
14	8½ yr.	9 yr.	1 wk.	3 mo.	0	0	+	+	0	+	Abdominal pain moderately severe; first evidence of cirrhosis, large abdomen (hepatosplenomegaly)
19	8 3/12 yr.	9½ yr.	2 days	16 mo.	0	0	0	+	0	0	Initial symptoms 1 mo. after mother had icterus and fever; many neighbors also had jaundice; older sister died of cirrhosis, after 7 mo. illness, 1 mo. before patient was ill
22	2 mo.	6 yr.	2 wk.	6 yr.	+	0	0	0	0	0	
23	12 yr.	14 yr.	2-3 days	See remarks; 21 mo.	(+)	+	+		(+)	+	Symptoms 21 mo. before diagnosis of cirrhosis; bouts of fever since; jaundice and acholic stools for 16 mo. before admission
24	13 yr.	14 yr.	Continue 16 mo.	16 mo.	+	0	0	+	+	—	Ascites, edema, and palpable spleen occurred 16 mo. after onset of the symptoms
27	10½ yr.	14 yr.	1 wk.	See remarks; (3½ yr.)	0	+	+	+	0	+	Biopsy; onset of cirrhosis indefinite; fever, fatigue, upper abdominal pain, anorexia, and hepatosplenomegaly at 10½ yr.; improved; spleen and liver normal size; again fever, abdominal pain, hepatosplenomegaly at 14 yr.; biopsy at this time; two brothers had cirrhosis
28	4 wk.	3¼ yr.	Continue 2 2/12 yr.	2 2/12 yr.	+	+	+	0	+	0	Jaundice subsided but stools remained light; diarrhea and epistaxis developed; hepatosplenomegaly 2 2/12 yr. later

TABLE 2.—*Symptoms of Cirrhosis in Children*

Symptom	Cases, No.	Per Cent of Total
Bleeding tendency	18	67
Abdominal enlargement	17	63
Jaundice	13	48
Fever	12	44
Weakness, listlessness, or fatigue	11	41
Loose, frequent stools	11	41
Abdominal pain	10	37
Light-colored stools	10	37
Anorexia	9	33
Loss or gain of weight	9	33
Anemia	9	33
Peripheral edema	8	30
Vomiting	7	26
Dark urine	7	26
Pallor	6	22
Irritability, nervousness	5	19
Drowsiness	4	15
Nausea	4	15
Rectal bleeding (without hematemesis)	4	15
Hematemesis	3	11

companying hepatomegaly) while two had only an enlargement of the liver (without accompanying splenomegaly). At necropsy, in comparison with tables of normal weights (Coppoletta and Wolbach) this hepatic enlargement was actually less marked than it appeared to be on clinical examination.

The high incidence of neurologic signs is of interest. These gradually progressed from the early signs of irrationality, restlessness, disorientation, and lethargy to coma, which gradually deepened, with the accompanying appearance of neurologic signs such as spastic rigidity; pyramidal signs, including the Babinski reflex and ankle clonus; nuchal rigidity, twitching, and convulsions. Death supervened within a few days in each of the 12 cases which showed any of these signs. In three cases a fever initiated this chain of events; in two cases hematemesis was the precipitating factor.

TABLE 3.—*Clinical Findings*

Signs	Cases, No.	Per Cent of Total
Splenomegaly	23	85
Hepatomegaly	21	78
Ascites	18	67
Jaundice	18	67
Evidence of probable collateral circulation	17	63
Distended superficial abdominal veins	11	41
Clinical hemorrhage	11	42
Hematemesis alone	5	19
Melena alone	1	4
Hematemesis and melena	5	19
Esophageal varices	2	7
Peripheral edema	12	44
Neurologic disturbances (terminal)	12	44
Bleeding tendency (aside from clinical hemorrhage)	10	37
Nevi	10	37
Clubbing of fingers	3	11

TABLE 4.—*Frequency of Jaundice in Twenty-Seven Cases of Juvenile Cirrhosis*

Jaundice	Cases, No.	Per Cent of Total 27 Cases
As initial symptom	12*	44
During course of illness (history)	14	52
During first examination at clinic	15	56 } 67
After first examination at clinic	3	11 }
Sometime during life	21	78

* The jaundice noted occurred in the neonatal period in only one case (Case 8).

Even if improvement occurred, as was seen in one patient, such improvement was only temporary, coma and death eventuating within a few days.

Twenty-one (78%) of these children with cirrhosis had jaundice at some time during life (Table 4). This includes episodes of jaundice which seemed from the standpoint of the history to represent episodes of acute hepatitis.

Laboratory Findings.—These are presented in Table 5. It might be pointed out that, whereas 12 of the patients had total protein values less than 6.5 gm. per 100 ml. of serum, only one child had a value less than 5 gm. per 100 ml. Four of the children had values more than 8 gm. per 100 ml. (8.1, 8.2, 8.9, and 10.7 gm.).*

In some instances the reversal of the albumin-globulin ratio represented actual decrease in albumin as well as increase in globulin. In others the albumin value was within normal limits and the globulin values were increased.

Elevation of the direct-reacting bilirubin to a greater degree than the indirect form was more frequent than the reverse condition. In cases in which only the total bilirubin and the van den Bergh reaction were recorded, the latter was more often direct than indirect.

Prognosis.—Table 6 charts the duration of life after the onset of the signs of cirrhosis, eliminating from consideration any

* Bergstedt and Lingen (Acta paediat. 46:185-190 [March] 1957) have reported two cases of cirrhosis of the liver in children who had hyperproteinemia, one having a value of 11.5 gm. and the other of 10.0 gm. per 100 ml.

TABLE 5.—*Laboratory Findings*

Laboratory Test	Positive Cases, No.	No. Examined	Per Cent Positive
Blood			
Macrocytosis on blood smear	13	25	52
Hemoglobin below 11.0 gm./100 ml.	12	26	46
RBC below 3,500,000/cu. mm.	16	27	59
Leukopenia: WBC below 5,000/cu. mm.	12	27	44
Platelets below 125,000/cu. mm.	10	18	56
Serum proteins below 6.5 gm./100 ml. serum	12	20	60
A/G ratio below 1.5/1.0	15	20	75
Urea over 35 mg./100 ml. serum	4	16	25
Bilirubin elevated	22	23	96
Direct alone increased: over 0.2 mg./100 ml. serum	2	16	12
Indirect alone increased: over 0.6 mg./100 ml. serum	2	16	12
Both direct and indirect increased	11	16	69
Direct increased more than indirect	10	16	62
Indirect increased more than direct	1	16	6
Total value alone recorded and this increased: over 0.8 mg./100 ml. serum	6	7	86
Van den Bergh direct	4	7	57
Van den Bergh indirect	2	7	29
Bleeding time increased: over 5 min.	2	12	17
Coagulation time increased: over 6 min. (capillary blood)	6	9	67
Urine			
Albuminuria	21	26	81
Microscopic hematuria (no gross hematuria)	10	26	38
Urine urobilinogen and urobilin	6	6	100
Urine bile	5	6	83
Stool: steatorrhea	2	3	67
Esophageal varices	2	13	15
Hepatic function tests			
Sulfobromophthalein retention	15	16*	94
Cholesterol below 120 mg./100 ml. serum	5	17	29
Cholesterol esters below 60% of total cholesterol	8	11	73
Alkaline phosphatase high	2	2	100
Prothrombin time over 19 sec.	19	23	83
Cephalin-cholesterol flocculation 3+ or more	4	10	40
Thymol turbidity over 4 units	3	7	43

* Seven were jaundiced at the time of the test.

preceding episode of presumed hepatitis. It should be emphasized that 18 patients (78% of the 23 patients who died) died in two years or less after the onset of the signs of cirrhosis.

Immediate Causes of Death.—Twenty-three of the twenty-seven patients who had histologically proved juvenile cirrhosis have died. The immediate cause of death could be determined in 20 (Table 7). The data available were insufficient to determine the causes of death in three. Two of the twenty-seven are still alive following their examination at the clinic, two years and six years ago, respectively. Attempts to follow the course of two patients since they left our care have been unsuccessful.

TABLE 6.—*Duration of Life After Onset of Cirrhosis*

Duration of Life	Cases, No.
1 mo.–6 mo.	8
7 mo.–12 mo.	3
13 mo.–2 yr.	7
2 1/12 yr.–4 yr.	2
4 1/12 yr.–6 yr.	2
6 1/12 yr.–8 yr.	1
Average, 21 mo.	

Gross Pathologic Aspects.—The gross pathologic findings are summarized in Table 8. In 12 cases there was blood in the stomach at necropsy, and in 1 case, in the intestine, while in only 6 cases were there esophageal varices. A ruptured varix was found in only one instance.

All the spleens were enlarged. The weights of the spleens ranged from 1.5 to 14.2 times the normal weight for the patient's age; the average weight was 5.8 times the normal.

The weight of the liver in each case, compared with the normal weight of the liver for the patient's age, ranged from 0.4 to 2.0 times normal. The average weight was 1.2 times normal. Stated differently, the weights of 15 (79%) of the 19 livers were

TABLE 7.—*Causes of Death in Twenty Cases of Juvenile Cirrhosis*

Cause of Death	Cases, No.	Per Cent of 20 Cases
Hepatic insufficiency	15	75
Gastrointestinal hemorrhage	11	55
Intercurrent infection	7	35

TABLE 8.—*Gross Observations (Excluding Liver) at Nineteen Necropsies*

Observations	Cases, No.	Per Cent of 19 Necropsies
Spleen		
Enlarged (50% more than normal weight)	16	84
Spleen surgically removed	3	16
Ascites	15	79
Hydropericardium	10	53
Hydrothorax	8	42
Peripheral edema	7	37
Evidence of hemorrhage in gastrointestinal tract	13	68
Jaundice	11	58
Evidence of collateral circulation	7	37
Esophageal varices	6	32
Other evidence of bleeding (petechiae, ecchymoses, etc.)	11	58
Kidneys		
Bile-stained	6	32
Enlarged (50% more than normal weight)	13	68

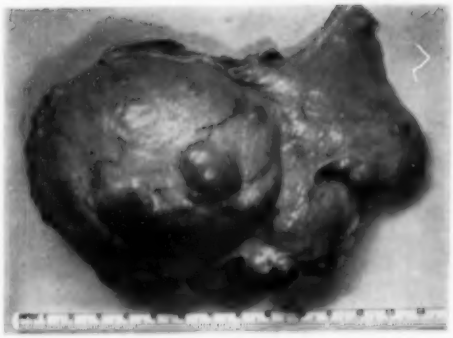

Fig. 1.—Cirrhosis of the liver in children. Lobar type.

either normal or more than normal for age.

Sixteen livers were available for study, and these were classified as lobar, nodular, and granular on the basis of the size of the regenerative nodules.

Lobar Type: The two cases in this group had massive regenerative nodules (Fig. 1). One of these livers had an extremely large regenerative nodule, approximately the size of a hepatic lobe. The other liver was less striking; it had a number of large regenerative nodules, each of which was smaller than that described for the other liver. All of these regenerative nodules (or "lobes") were huge, and their shapes were variable. These livers had broad deep bands of atrophic tissue between these huge nodules.

Nodular Type: The majority of the regenerative nodules of the eight livers in this group ranged from 0.5 to 2.0 cm. in diameter (Fig. 2). However, the diameter of some was slightly smaller and of others slightly larger than these dimensions. The distribution of the nodules also was variable. Within the same liver there might be a collection of large nodules in one area, a collection of small nodules in another, and an admixture of large and small nodules in a third area. In other areas there might be isolated small or large nodules. The smaller nodules were often arranged in clusters which presented an appearance on the sur-

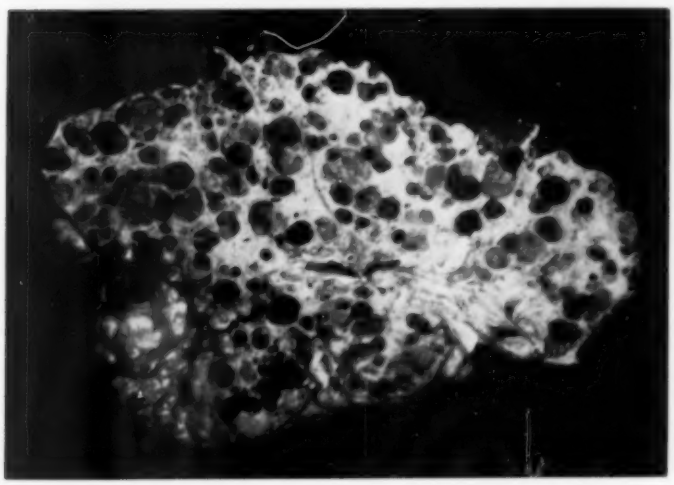

Fig. 2.—Cirrhosis of the liver in children. Nodular type. Cut surface. Note distortion of veins by regenerative nodules.

face of one large regenerative nodule. Marked distortion of the venous radicles by these large regenerative nodules was often seen grossly (Fig. 2). The size of the atrophic zones of connective tissue was similarly variable. There were many wide bands of atrophic tissue up to 2.5 cm. or more in width (Fig. 2). These were in general wider than the connective-tissue bands in livers of the granular type. There were some atrophic areas on the surface several centimeters in greatest diameter, consisting only of connective tissue and no parenchymal (regenerative nodular) tissue.

There was one exception, in the nodular group, to this gross description. The liver in Case 25 had regenerative nodules which varied from 1 to 9 mm. in diameter. However, these nodules were so clustered in groups at the surface that they gave the surface appearance of nodules from 3 mm. to 2.5 cm. in diameter. This structural characteristic was typical of the nodular group as a whole. The unusual feature of this particular case was the absence of wide zones of atrophy in the areas between the regenerative nodules. The nodules were all pressed closely together. In fact, these extremely narrow bands of connective tissue sharply differentiated this case, in gross appearance, from all of the other 15 livers examined grossly. The other livers all had atrophic zones and connective-tissue bands which were fairly wide, although the width varied from case to case and within the same liver.

Granular Type: In the six livers of this group most of the regenerative nodules were less than 5.0 mm. in diameter (Fig. 3). Many of the nodules were approximately 3 to 4 mm. in diameter. There were a few larger nodules, and rare nodules up to 1 cm. in diameter could be found on careful search. The granular pattern caused a less obvious gross venous distortion. In this group there were also wide bands of atrophy, which were noted in all of the other grossly examined livers except that in Case 25. The nodules, as in the cases in the other groups (except Case 25), were close together in some areas and far apart in

Fig. 3.—Cirrhosis of the liver in children. Granular type. Cut surface. Small regenerative nodules but wide bands of internodular stroma.

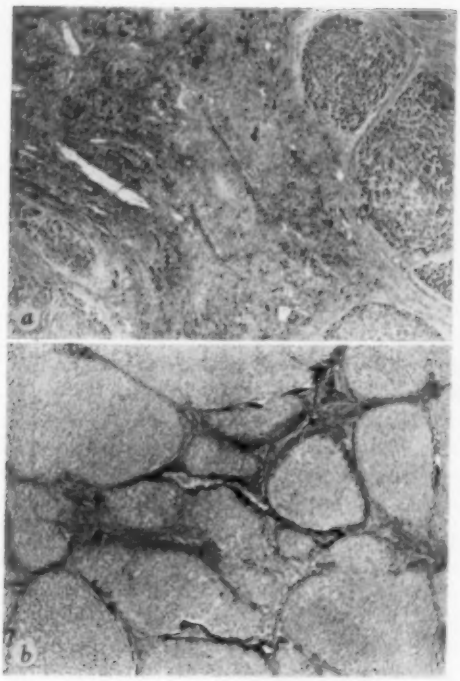

Fig. 4.—Cirrhosis of the liver in children. (*a*) Wide bands of internodular stroma. Hematoxylin and eosin; ×30. (*b*) Distortion of veins by regenerative nodules. Elastic-Van Gieson stain; reduced about 30% from mag. ×30.

other areas, with intervening bands of connective tissue up to 1.5 cm. wide. On the surface there were wide areas, up to 4.5 cm. in greatest diameter, consisting only of collapsed stroma.

Histologic Study.—The livers in all of the 27 cases except one (Case 25) exhibited the same general histologic pattern. Therefore these 26 similar cases are conveniently discussed as one group.

General Structural Pattern: The normal histologic pattern of the liver was altered in every instance. There were three major features typical of this altered pattern. Regenerative nodules were observed in every case, and the size of these nodules varied within the same section or in different sections from the same liver. The second feature was the wide bands of connective tissue (collapsed stroma) (Fig. 4*a*). Throughout the sections these bands of collapsed stroma coursed between the regenerative nodules in a completely irregular manner. In some specimens these connective-tissue bands were so wide that, when a section was made, only connective tissue appeared; no regenerative parenchymal nodules were seen in such sections. The third major feature was the distortion and apparent compression of the venous channels in the internodular stroma (Fig. 4*b*). This venous distortion was apparently secondary to the growth of the neighboring nodules. Within the regenerative nodules themselves, a central vein was not seen in the great majority of cases. When a central vein was identified within a nodule, the vein was often distorted in shape and always eccentric in position.

Regenerative Nodules: The regenerative nodules were often distorted in shape by neighboring nodules. Fairly narrow bands of connective tissue with leukocytic infiltration were frequently seen to extend partially into the nodules from the internodular stroma. The outlines of the nodules were sharply delineated in some areas but poorly delineated in other areas of the same liver or even in the same section. This poor delineation was the result of either a dense leukocytic infiltration at the periphery of the nodule continuous with the internodular stroma or a peripheral zone of loosely arranged hepatic cells and connective tissue. In many instances the nodule consisted of many small islands of hepatic cells lying in a connective-tissue framework of collapsed stroma. This entire mass, containing many islands of hepatic cells, was completely encircled by connective tissue. Such an arrangement probably represents an early phase in the development of the regenerative nodule.

Intracytoplasmic hyaline bodies were present in only 2 of the 26 cases. These bodies were present in areas which showed fairly marked evidence of nuclear and cytoplasmic degeneration. Infiltration of the hepatic parenchyma with fat was present in 12 cases, but in no instance was this infiltration of any marked degree. No large

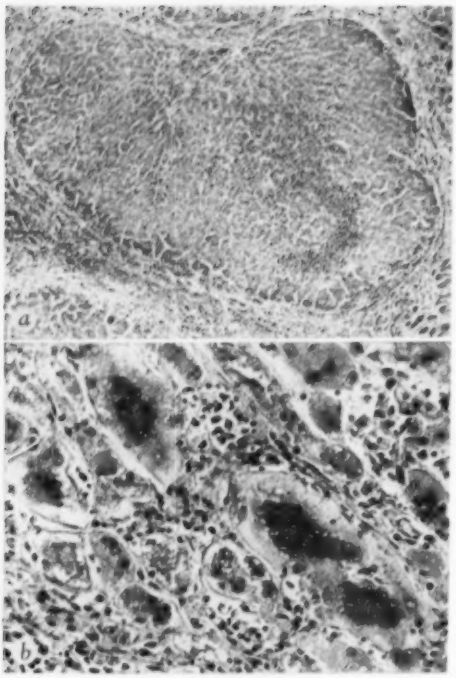

Fig. 5.—Cirrhosis of the liver in children (*a*) Degeneration and necrosis of hepatic cells within a regenerative nodule. Hematoxylin and eosin; reduced about 30% from mag. × 60. (*b*) Multinucleated giant parenchymal cells of a regenerative nodule. Hematoxylin and eosin; reduced about 30% from mag. × 200.

fatty cysts were observed in any of the sections. Pigment granules were present within the cytoplasm of the hepatic cells in 20 cases.

The cells within the nodules revealed two major types of changes: degenerative and regenerative. Often examples of these two types of changes were apparent within the same microscopic field. Cytoplasmic evidences of degeneration were cytoplasmic acidophilia (often with small pyknotic nuclei) and cytoplasmic vacuolization. The nuclear degenerative changes that were noted, in addition to pyknosis, were karyolysis and, very rarely, karyorrhexis. The areas of degeneration varied greatly in size. Often such areas were found to occupy a portion of a regenerative nodule (Fig. 5*a*). Concomitant evidences of regeneration were also widespread. Mononuclear and binuclear giant cells were frequently seen (Fig. 5*b*). Such cells often assumed a bizarre shape and occasionally contained numerous nuclei. Another sign of regenerative activity was the almost uniform presence of hepatic cells arranged in parallel laminae, two cells in thickness. The Kupffer cells were increased in 24 of the 26 cases. Bile pigment was found within the Kupffer cells in 16 cases.

Leukocytic parenchymal infiltration was seen in all but two cases. This was usually mononuclear in type, although varying degrees of polymorphonuclear-cell infiltration were also seen. The polymorphonuclear infiltration was the predominant type in only three cases, and in many cases the mononuclear infiltration was the only type noted.

Internodular Stroma: In general, the connective tissue consisted of collapsed stroma which had become condensed. The bile ductules were considered to be increased in number in 18 of the 26 cases. Leukocytic infiltration of this internodular stroma was present in all cases and was mononuclear in all but one. In this one, there was a somewhat greater number of polymorphonuclear leukocytes than of mononuclear leukocytes. In some of the other cases some polymorphonuclear leukocytes were present in the internodular stroma, although the mononuclear infiltration was of a much greater degree. Plasma cells were also occasionally seen. This internodular infiltration was increased in the periductal area in only four of the cases.

Vascular Changes: The venous compression and distortion have already been noted. The diffuse internodular leukocytic infiltration was increased in the perivascular areas in only two cases.

Spleen: Splenic tissue was available for microscopic study in 19 cases. All revealed a similar histologic picture. The Billroth cords were wider than normal, owing to the presence of increased connective tissue, which was often fairly compact and collagenized. The Billroth cords had a decreased number of erythrocytes. The capsule of the spleen was frequently thickened, and the

trabeculae were practically uniformly increased in number. The borders of the trabeculae lost their normally sharp definition as the trabecular connective tissue merged into the connective tissue of the surrounding pulp (*Trabekelaufsplitterung*).[25] The Malpighian bodies were practically always reduced in size and in number and had an associated perifollicular fibrosis or a perivascular fibrosis of the central artery or both.

Kidneys: The kidneys of 17 of the 27 patients were examined histologically. The most frequent changes noted were focal glomerulitis manifested by endothelial proliferation in the glomerular capillaries (11 cases), hyalinized glomeruli (4 cases), hydropic degeneration of the cells of the proximal and distal convoluted tubules (10 cases), and leukocytic interstitial infiltration (9 cases), which was usually lymphocytic, focal, periglomerular, and perivascular. More than one type of change was noted in some kidneys. The high frequency of kidneys with histologic abnormalities (94% of 17 cases) is considered worthy of special note.

Adrenal Glands: Sections of the adrenal glands stained with hematoxylin and eosin were available for histologic study in 14 cases. The adrenal glands in 12 cases were thought to have a decreased amount of lipid in the cortex, but this could not be determined with certainty, because the sections had been stained only with hematoxylin and eosin.

None of the other organs or tissues obtained at necropsy consistently revealed any significant pathologic changes.

Comment

The most interesting feature of this study is the convincing evidence, both clinical and pathologic, that viral hepatitis plays an important and perhaps dominant role in the causation of cirrhosis of the liver in these children. This evidence may be recapitulated briefly as follows: 1. There was a high incidence (15 of 27 cases, 56%) of a disease process with clinical manifestations of viral hepatitis as a precursor of the cirrhosis. It is important to recognize also that in the remaining 12 cases the clinical histories did not exclude a preceding hepatitis; they merely did not contain sufficient data to justify such a diagnosis. 2. There was a high incidence of a preceding or coincidental jaundice. Stauffer and one of us,[1] in a comparative study of posthepatitic and Laennec's cirrhosis, found a higher incidence of jaundice in the posthepatitic form. However, in evaluating such data (indicative of a possible antecedent attack of hepatitis)[15] one must remember that the frequency of hepatitis unaccompanied by icterus is unknown. To add to the difficulties of assessing the history, an antecedent attack of jaundice may not represent an antecedent attack of hepatitis. 3. There was no history of alcoholism or any evidence of malnutrition. 4. There was no history of exposure to hepatotoxins. 5. In all but one case the liver had the gross and histologic appearance of postnecrotic[17] or toxic[23] cirrhosis or multiple nodular hyperplasia.[24] These terms all signify a morphologic type of cirrhosis that is the commonest variety produced by viral hepatitis.[1,14,32,39]

In general, these cases resembled posthepatitic cirrhosis as observed in adults at necropsy in the high incidence of jaundice and of hemorrhages, in the low incidence of esophageal varices, and in the gross and histologic appearance of the liver. They resembled Laennec's cirrhosis in adults in the high incidence at necropsy of ascites, of splenomegaly, and of hypertrophy of the liver.

Evidence that viral hepatitis may occasionally lead to cirrhosis of the liver has been increasing significantly over the years.[1,4-6,13,14,18,19,21,27,30,35,36,38,39] A classic article dealing with the transition of hepatitis to cirrhosis is that published by Jones and Minot in 1923. They reported data on three patients, each of whom had an acute illness with jaundice, gastrointestinal disturbances, fever, and malaise, and in each of whom histologically proved hepatic cirrhosis had

developed in 6 weeks to 16½ months. By needle biopsy of the liver in severe and protracted or relapsing cases of hepatitis, many workers have been able to demonstrate histologically a gradual transition from ordinary acute hepatitis to fully developed cirrhosis.[13,14,18,35,36,38] The morphogenetic sequences of the cirrhosis that develops from hepatitis have been well outlined by Thaler. Most of these studies supporting the contention that hepatitis may give rise to cirrhosis have been made on adults.[18,28] However, Laurie, in 1935; Stokes and associates and Schindler and Kindschi, in 1951; Craig and Landing, in 1952; Dible and associates,[12] in 1954, and Craig, Gellis, and Hsia, in 1955 have linked juvenile hepatitis and histologically proved juvenile cirrhosis, while Bellin and Bailit reported a case in which histologically proved portal cirrhosis occurred in a newborn infant of a mother who had presented the symptoms of infectious hepatitis two months before term.

In our cases all biopsies were wedge biopsies. Many investigators [29,33,37] have reported on the inaccuracy of needle biopsy for the diagnosis of postnecrotic cirrhosis. They generally agree that, although the needle-biopsy specimen may represent well diffuse liver-cell damage or diffuse infiltration with fat, it often fails to present clearly the alterations of the lobular pattern, scarring, and inflammatory changes. These are the features that are important to the pathologist who attempts a differential diagnosis between postnecrotic and Laennec's cirrhosis.

The liver weights in the present series of cases were generally normal or above normal for the patient's age. One of us and Stauffer found that the liver in posthepatitic cirrhosis is generally smaller than normal, while the liver in alcoholic cirrhosis is generally larger than normal. The discrepancy in the present series of cases may be accounted for by the fact that in children hepatic regeneration may be more vigorous and give rise to livers that are normal or larger than normal in spite of a severe destructive process. It has been demonstrated repeatedly that experimental regeneration after hepatectomy is much more vigorous in young than in adult animals.[23]

The frequency of occurrence of renal lesions in patients having cirrhosis and other hepatic lesions has been previously reported.[2,7,11,26]

Reference to Table 5 reveals that the high incidence of abnormal renal histologic and laboratory findings in the present series correlated poorly with the clinical findings.

Summary and Conclusions

A clinicopathologic study of 27 cases of juvenile cirrhosis revealed that in 15 cases (56%) the history was compatible with a preceding hepatitis.

The gross appearance of 15 of the 16 livers in which either adequate specimens or adequate photographs were available for study was consistent with a diagnosis of postnecrotic or posthepatitic cirrhosis. The gross appearance of the liver in one case (Case 25) was consistent with a diagnosis of Laennec's cirrhosis.

The histologic characteristics of 26 of 27 livers were in general agreement with the histologic criteria established for the diagnosis of posthepatitic cirrhosis.

There is, therefore, clinical evidence in 15 and pathologic evidence in 26 of these 27 cases for the conclusion that a preceding hepatitis was the initiating event in the pathogenesis of the cirrhosis.

In 16 of the 17 cases of juvenile cirrhosis in which histologic examination of the kidneys was performed, the examination revealed variations from the normal. These consisted of focal glomerulitis, focal hyalinized glomeruli, hydropic degeneration of the cells of the proximal and distal convoluted tubules, and lymphocytic infiltration of the interstitium. These changes correlated poorly with the clinical findings.

Mayo Clinic.

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Case Reports

Acute Hemolytic Anemia in the Neonatal Period

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This paper reports the occurrence of acute hemolytic anemia in the neonatal period secondary to naphthalene poisoning. The route of absorption of the toxic material from clothing and diapers makes this report of exceptional interest to pediatricians and general practitioners dealing with infants.

The diagnosis of acute hemolytic anemia in the neonatal period is primarily the differentiation of intrinsic from extrinsic etiologic factors. Most frequently encountered are the intrinsic factors. These include hemolytic disease of the newborn due to Rh and ABO incompatibilities, congenital syphilis, thalassemia, and the other rare hemoglobinopathies.

The group of hemolytic anemias caused by extrinsic factors is expanding rapidly. Recently Wintrobe listed acute hemolytic anemia following vaccination, gas poisoning, and cranberry ingestion with 52 previously identified causes.[1] Very recently, Cunningham reported several cases of acute hemolytic anemia in newborn infants secondary to absorption of resorcinol in skin lotions.[2]

Scattered throughout the literature are many reports of undiagnosed acquired hemolytic anemia, or Lederer's anemia, which suggest still other agents not specifically identified by history or laboratory findings.[3]

Report of Case

An 11-day-old Chinese boy was admitted to Children's Hospital of the East Bay on July 23, 1956, because of jaundice and lethargy. He was the product of an eight-month uncomplicated gestation and a spontaneous controlled delivery. Birth weight was 6 lb. 4½ oz. The patient was dismissed from the hospital of birth to home on the fourth postpartum day in good condition. At home, the baby became progressively lethargic, and after approximately seven days, he developed icteric skin and sclerae. Dark urine and pallor were also noted by the parents. The jaundice increased progressively up to the time of admission. The child continued to take his formula satisfactorily, and bowel movements were reported as normal in number, color, and consistency. The infant's clothes and diapers were reported to have been stored in mothballs for several years and neither aired nor washed prior to use.

Physical examination on admission: The patient was a well-developed well-nourished 11-day-old Oriental boy in acute distress, with rapid shallow respirations. The skin was markedly icteric, but it was warm and of good turgor. The sclerae were icteric. Fontanels were patent, without signs of altered pressure. Heart and lungs revealed no abnormality. The liver was palpable 4 cm. below the costal margin, and the spleen was palpable 4 to 5 cm. below the costal margin. The urine grossly on admission was dark and had a pungent odor.

Laboratory studies on admission: Coombs' test was negative. Mother's blood, Type A2, Rh-positive. Baby's blood, Type O, Rh-positive. Hemoglobin on admission was 4.5 gm.; red cell count, 1,100,000. The peripheral smear revealed 51 nucleated red blood cells per 100 white blood cells (3 blast cells, 14 pronormoblasts, and 34 normoblasts). The red cells showed extreme fragmentation, occasional Heinz bodies, and marked aniso- and poikilocytosis. The white blood cell count was 64,000, with all cells appearing toxic. Differential count showed 4% blastcells, 2% eosinophils, 3% myelocytes, 8% juvenile cells, 25% stabcells, 28% segmented cells, and 20% lymphocytes. The admission urinalysis revealed one to three white blood cells per high-power field and a trace of bile and was negative for urobilinogen. The total bilirubin on admission was 20.7 mg. per 100 cc.; serum hemoglobin was 64.4 mg. per 100 cc. Unfortunately, specimens for chemical analysis

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were obtained after withdrawal of diaper contact and initial therapy. Determinations of alpha-naphthol levels were not done, and by this time the tests for betanaphthol were negative. Electrophoretic studies of the serum showed increased α_1- and α_2-globulins.

After preliminary work-up, the baby was given 60 cc. of type-specific whole blood by push transfusion. Blood for cultures, which proved to be negative, was drawn prior to transfusion. The child was given antibiotics, oxygen therapy, and oral feedings. On July 24 the red blood cell count was found to be 2,900,000; white blood cell count, 30,000, and hemoglobin level, 9.7 gm., with 11.5% reticulocytes. The hematocrit value was 25%, and the serum bilirubin was 16.3 mg. per 100 cc. On July 25, 50 cc. of type-specific whole blood was again given. The hemoglobin was 9.1 gm.; the packed cell volume, 28%, and the serum bilirubin, 10.5 mg. per 100 cc. On July 26 the serum bilirubin was 7.9 mg. per 100 cc. and the hemoglobin was 10.2 gm. The serological tests for syphilis were reported negative on this date. On the day of dismissal, July 30, 1956, the hemoglobin was reported as 10.8 gm.; the packed cell volume, 30%, and the serum bilirubin, 3.6 mg. per 100 cc.; white blood cell count was 8800, with a normal differential.

The infant has been followed at weekly intervals, with the hemoglobin remaining stable and the child developing and gaining weight normally. The clinical diagnosis of hemolytic anemia due to naphthalene absorbtion from the diapers appears to be clear in view of the history of contact, odor of naphthalene in the urine, and rapid permanent recovery after withdrawal of contact and treatment.

Comment

Acute hemolytic anemia due to naphthalene intoxication was first reported by Zuelzer and Apt, in 1949.[4] Schafer,[5] in 1951, reported a 6-day-old girl who had been admitted to the hospital because of jaundice and cyanosis of several hours' duration. Findings were suggestive of congenital heart disease and physiologic jaundice. However, review of the history revealed that the diapers had been stored for months in mothballs and although "thoroughly" rinsed still "reeked" of the mothballs at the time of admission.

In the hospital, the patient's urine became dark red; the hemoglobin, markedly reduced, and she went into shock. Treatment included warmth, plasma, whole blood, and caffeine and sodium benzoate. There was temporary improvement, then a rapid downhill course with death. Postmortem examination showed (1) small focal hemorrhages in the lungs and bladder; (2) extramedullary hematopoiesis in the heart, liver, spleen, and adrenals; (3) gross and microscopic hemoglobin in the kidney tubules. The conclusion reached was that the absorption of the naphthalene residual in the diapers occurred through the skin, producing an acute hemolytic anemia.

Mackell and Bauer[6] reported experimental studies of naphthalene-induced hemolysis from which they concluded that cell fragmentation is the essential pathologic process and acute massive intravascular hemolysis the fatal end-result. Rieders and Brieger[6] have shown by in vitro experiments that the true hemolytic agent is not naphthalene but actually its oxidative metabolites (alphanaphthol, betanaphthol, α-naphthoquinone, β-naphthoquinone). In vivo, only alphanaphthol showed hemolytic activity. These findings were substantiated clinically when Mackell and Bauer isolated alphanaphthol in the urine of a patient with acute hemolytic anemia known to be due to naphthalene poisoning.

The treatment of this condition is primarily supportive. Replacement of the hemolyzed blood by whole blood or packed cells is the urgent need. The threat of lower nephron nephrosis is great where hemoglobinemia is pronounced. Zuelzer and Apt recommend alkalinization of the urine by use of lactate or bicarbonate.

Therapeutic procedures warranting further evaluation include exchange transfusion to provide for removal of hemolytic agents and replacement of cells and to prevent the development of kernicterus where the serum bilirubin concentration is above the known safe values.[7] Corticotropin (ACTH) and cortisone have also been used, but without adequate controls essential to establish their value.[8]

Recent experimental work has shown that plasma, cholesterol, and lecithin do not inhibit hemolytic activity of the naphthalene

metabolites in vitro.[6] These agents have not been used therapeutically.

Summary

A case is presented of acute hemolytic anemia apparently due to naphthalene intoxication as a result of absorption from diapers which had been stored in mothballs. Recovery after intermittent whole blood transfusions has been complete. Other therapeutic procedures are reviewed and discussed.

It is possible that the occurrence of this type of complication has been more frequent than has been realized. Awareness of physicians and parents of the danger of storing infant clothing in mothballs is an apparent need.

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Fatal Accidental Poisoning by Aminophylline in a Child

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Fatal poisoning from ingestion of aminophylline or other xanthines is uncommon. Large doses are apparently required to produce death. The fatal dose of caffeine in man is estimated to be about 10 gm.,[1] while the LD_{50} for aminophylline in mice has been variously reported at 265 mg. per kilogram [2] to 540 mg. per kilogram of body weight.[3]

Previous to this year 10 cases of aminophylline toxicity in children, all of whom recovered, had been reported.[4,5] This year 10 additional cases were reported by one observer, 4 of whom died.[6] A fatality has been reported in a child from accidental consumption of an antiasthmatic preparation containing racephedrine (Ephedrine) hydrochloride, theophylline, and phenobarbital, in which it was thought that the theophylline acted as a potentiator for the racephedrine.[2] Intravenous injection of therapeutic amounts of aminophylline has been followed by sudden death, but the mechanism here is postulated to be a direct effect on the heart, with cardiac standstill or ventricular fibrillation,[7] and usually is reported only in patients with preexisting cardiac disease.

It is our purpose to report a case of fatal poisoning following the accidental ingestion of 3 gm. of aminophylline by an 18-month-old child, a dose of 307 mg. per kilogram of body weight.

Report of Case

An 18-month-old Negro girl was admitted to the hospital on April 11, 1956, with a history of convulsions. The history as obtained from the mother revealed that the child had been in previous good health until a day prior to admission, when between 1 and 3 p. m. the child, having been left alone for a short time, accidentally ingested 3.2 gm. of enteric-coated aminophylline, which had been prescribed for the grandmother. In addition to sixteen 200 mg. aminophylline tablets, an unknown but small quantity of rauwolfia serpentina probably was swallowed. When the mother discovered that the child had eaten the tablets, she called the grandmother's physician to inquire about possible danger to the child. She was told that if the child seemed all right and was not vomiting there would be nothing to worry about. At about 9:30 a. m. the next day the child vomited several times and seemed somewhat irritable. The child was taken to the office of one of us and was noted to be listless and cyanotic, with tachycardia and rapid, shallow respirations. During the examination she had a generalized convulsion. She was immediately hospitalized for treatment.

On admission, physical examination revealed a well-developed, adequately nourished Negro girl of 18 months, who lay unresponsive to painful stimulation and was cyanotic. The extremities were held in tonic extensor spasm, and every several minutes there were generalized clonic convulsions. The pupils were widely dilated but responded to light. Gag reflex was present. There was sinus tachycardia and diffused bronchial rhonchi throughout all lung fields. There was considerable abdominal distention, believed to be due almost entirely to gastric dilatation. Temperature was 105.0 F rectally, pulse rate 160, BP 120/60. Questionable nuchal rigidity was noted. The respirations were rapid and shallow.

Immediate therapy consisted of oxygen by mask and later by tent. Gastric lavage was performed, with a copious amount of brown fecal-smelling gastric contents and some undigested food particles being recovered. An intravenous infusion of 5% dextrose in water was started by cut-down in the ankle. Penicillin and streptomycin were begun. Sodium phenobarbital, 100 mg., was given intramuscularly

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and 30 mg. repeated at fairly frequent intervals in an attempt to control the convulsive seizures. Lumbar puncture revealed normal spinal fluid with no cells. Laboratory studies revealed a hemoglobin of 9.0 gm., RBC 3,150,000, WBC 43,000, with 88% polymorphonuclears, 12% lymphocytes, and a marked shift to the left.

The child continued to convulse as described above, despite the barbiturates. Rectal instillation of 50% ether in liquid petrolatum emulsion (mineral oil) was given and was repeated at 1½- to 2-hour intervals. The intensity of the convulsive seizures decreased, but the extensor tonus persisted. The general condition of the patient remained unchanged. At midnight the child voided spontaneously for the first time since admission. The specimen could not be obtained for study. Shortly thereafter the child's respirations became more labored and respirations ceased at 12:10 a. m. on April 12, 1956. Artificial respiration was to no avail, and the patient was pronounced dead at 12:20 a. m.

An autopsy was performed nine hours after death. There was slight distention of the abdomen. The right lower leg showed a moderate degree of edema probably due to infiltration of infusion fluids. Peritoneal cavity contained approximately 200 cc. of a thin brownish fluid. The liver edge extended below the costal margin 3 cm. on the right, 3 cm. in the middle, and 3 cm. on the left. The pleural and pericardial cavities contained no fluid or gas. The lungs appeared slightly increased in size and weight. The parenchyma of all lobes was reddish-gray in color and soggy in consistency. On pressure, a moderate amount of frothy serous fluid exuded from the cut surface. The bronchi and bronchioles were patent. The stomach along the greater curvature in the mid-portion showed a few small mucosal erosions. The transverse colon showed a moderate degree of dilatation. The remaining G. I. tract showed no particular gross abnormalities. In the brain the subarachnoid veins showed a marked degree of congestion. The gyri were flattened and the sulci narrowed. The ventral surface of the brain showed a marked conus of the cerebellum. Multiple coronal sections of the brain revealed no intrinsic gross abnormalities. The gross anatomical diagnosis was pulmonary edema and hyperemia, moderate bilateral and cerebral edema, with marked hyperemia.

On microscopic examination the lungs showed marked hyperemia, and the heart muscle showed a generalized cloudy swelling of the myofibrils with multiple foci of aseptic necrosis. The spleen showed marked passive hyperemia. The kidneys showed severe passive hyperemia and marked cloudy swelling; the liver showed moderate passive hyperemia; the brain showed moderate passive hyperemia. Sections of the pancreas and thymus were normal. Sections of the gastrointestinal tract were not reported.

Comment

Of the three drugs of therapeutic interest in the methylxanthine group, theophylline occupies an intermediate position in central nervous system stimulation. Caffeine is the most powerful central nervous system stimulant, followed closely by theophylline. Theobromine causes little central stimulation, its chief effect being on muscle. Cardiac stimulation and coronary artery dilatation are most pronounced with theophylline; theobromine and caffeine have weaker action in this regard. Theophylline has the strongest diuretic effect. Aminophylline contains about 87% theophylline combined with 13% ethylenediamine, representing about 75% anhydrous theophylline.

The reports of serious toxicity from aminophylline fall into two main groups: first, those patients with known cardiac disease who have received aminophylline intravenously and who experienced collapse and sudden death, in which the toxicity appears to be related to the cardiac muscle stimulation or coronary dilatation, with ventricular fibrillation and cardiac arrest; second, that group of patients who develop signs of toxicity relating to the central nervous system, gastrointestinal tract, and kidneys, with vomiting, restlessness, muscular twitching, convulsions, respiratory depression, gastrointestinal hemorrhages, and albuminuria. This type of toxicity has been reported most frequently in children. Six severe cases were reported by Rounds,[4] four milder cases by Love and Corrado,[5] and ten cases with four deaths by Nolke.[6] In our case therapeutic efforts were hampered by the delay in appearance of severe toxic symptoms due to the ingestion of enteric-coated tablets. By the time the aminophylline had begun to exert its toxic effect, there was no opportunity to remove it from the body. A lack

of appreciation by the first physician consulted of the potentially serious effect of this drug in children caused further delay. There being no specific antidote, therapeutic efforts must be limited to attempting to minimize the central nervous system damage and using general supportive measures. If the patient can be tided over the initial onslaught, apparently recovery is prompt and complete.

Aminophylline should be considered a dangerous drug and should be kept out of reach of children. Physicians should realize the potential dangers of this drug and be alerted in case of accidental ingestion. Since enteric coating delays the onset of toxic symptoms and therefore jeopardizes efficient treatment, and since there seems to be no marked therapeutic advantage in the use of enteric-coated aminophylline, it is further suggested that the use of plain aminophylline tablets be encouraged.

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Abstracts from Current Literature

Acta pædiatrica, Stockholm

45, No. 6 (Nov.) 1956

The Effect of the Ingestion of Potassium Salts on the Excretion of Sodium-Retaining Corticoids in the Human Subject. H. E. Wilson.—p. 589.

Acute Osteomyelitis in Infancy. B. Wolman.—p. 595.

* Erythrocyte Production and Iron Stores in Premature Infants During the First Months of Life. M. Seip and S. Halvorsen.—p. 600.

Les hématomes sous-duraux: Etude expérimentale. F. Girard.—p. 618.

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Histological Changes of the Pyloric Myenteric Plexus in Infantile Pyloric Stenosis: Studies on Surgical Biopsy Specimens. O. Steinicke-Nielsen.—p. 636.

Local Inhibition of the Tuberculin Reaction after Repeated Testing of BCG-Vaccinated Subjects. R. Berfenstam and K. E. Fichtelius.—p. 648.

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Proceedings of the Danish Pediatric Society, Jan. 28, 1956; Feb. 29, 1956; April 18, 1956; May 16, 19[illegible].—p. 659.

Proceedings of the Section of Pediatrics and School Hygiene of the Swedish Medical Society.—p. 665.

Erythrocyte Production and Iron Stores in Premature Infants During the First Months of Life.—A group of premature infants were studied during the first months of life by reticulocyte counts twice weekly, hemoglobin determinations and red blood cell counts weekly, and bone marrow studies for iron content approximately every four weeks. Rates of growth were also recorded. The usual trend of hemoglobin values was found, with a marked drop during the first eight weeks of life. Reticulocyte counts revealed high values for a few days after birth, falling to a low level at 1 to 2 weeks of age; this low level persisted for one to two weeks in the smallest infants and for three to four weeks in heavier prematures and was followed by a period of intensive reticulocyte formation. Little or no stainable iron was demonstrable in the marrow immediately after birth, but a marked increase occurred in the interval of four to eight weeks after birth; this deposit again decreased until no hemosiderin was found at 6 to 12 weeks of age. This disappearance of iron occurred earlier in smaller infants, occurring at 16 to 20 weeks of age in the full-term infant.

These data are discussed in relation to findings of other investigators and the theoretical concepts of the pathogenesis of the anemia of prematurity. It is concluded that the postnatal drop in hemoglobin is due to "(1) growth, (2) increased hemolysis, (3) a transient decrease in erythropoietic activity." It is felt that, contrary to other authors' views, the total hemoglobin begins to increase at 4 to 6 weeks in very small prematures and this soon leads to a state of iron deficiency. It is therefore advised that prematures be given supplemental iron, at 4 to 6 weeks of age in the case of very small prematures and at 6 to 8 weeks of age in the heavier ones.

American Heart Journal, St. Louis

53, No. 1 (Jan.) 1957

* Simultaneous Electrocardiograms in Thoracopagus Twins. Norman J. Johnson and James E. Doherty.—p. 150.

Simultaneous Electrocardiograms in Thoracopagus Twins.—Thoracopagus twins were studied to determine the feasibility of their surgical separation. The twins, having a common umbilical cord, were attached from the manubrium sterni to the umbilicus. Intravenous pyelogram revealed at least one functioning kidney in each of the twins, with some passage of the contrast media from one twin to the other. Although the livers were intimately

fused, each of the twins had a separate and apparently normal gastrointestinal tract. Angiocardiogram revealed the hearts to be fused, with a communication between a single ventricular chamber in one twin to a single ventricular chamber in the other. The single ventricle in each of the twins gave rise to a common arterial trunk in both subjects.

Standard Leads I, II, and III and a unipolar lead placed in the right scapular area were recorded simultaneously in the two subjects. These tracings revealed a common focus of activity for both hearts, with the complexes from both hearts occurring simultaneously. In addition, when the frontal plane QRS vectors were plotted it was found that the QRS axes were exact mirror images of each other. Only one other case of simultaneous electrocardiograms has been reported in thoracopagus twins, and that case differed from the one reported by these authors in that the electrical activity of the hearts was shown to be independent.

American Journal of Medicine, New York

21, No. 6 (Dec.) 1956

Hemochromatosis and Hemosiderosis: Does Iron Overload Cause Diffuse Fibrosis of the Liver? L. J. Rather.—p. 857.

The Latex Fixation Test: I. Application to the Serologic Diagnosis of Rheumatoid Arthritis. Jacques M. Singer and Charles M. Plotz.—p. 888.

The Latex Fixation Test: II. Results in Rheumatoid Arthritis. Charles M. Plotz and Jacques M. Singer.—p. 893.

Tumors Associated with Hypoglycemia—Pancreatic and Extrapancreatic. Milton R. Porter and Virginia Kneeland Frantz.—p. 944.

* Seizures in Infectious Mononucleosis: With a Review of the Literature. Harold P. Lazar, Roland Manfredi, and James H. Hammond.—p. 990.

Seizures in Infectious Mononucleosis: With a Review of the Literature.—Neurologic complications are reported as occurring in somewhat under 1% of all cases of infectious mononucleosis but as carrying a more severe prognosis, with an 11% mortality. On the other hand, seizures are an even rarer complication of infectious mononucleosis, there being only 14 reported cases including the 1 in the present report, and with this complication the outlook may be better, since there has been but one death. The age range of patients with convulsions complicating infectious mononucleosis was 8 to 24 years. The seizures, although generalized, had no characteristic pattern except that stupor or unconsciousness usually persisted for varying periods afterwards. The seizures preceded, coincided with, or followed the lymphadenopathy and splenomegaly. Examination of the spinal fluid showed increased protein with or without pleocytosis; in two instances the fluid had a positive heterophil anitbody titer. Recovery, in general, was prompt and complete, except that one patient had residual electroencephalographic changes. This report serves as a reminder to consider infectious mononucleosis in the differential diagnosis of unexplained and ill-defined seizures as well as of encephalitides.

American Journal of Pathology, Ann Arbor, Mich.

33, No. 1 (Jan.-Feb.) 1957

Histochemical Studies on the Cerebral Lipidoses and Other Cellular Metabolic Disorders. Benjamin H. Landing and David G. Freiman.—p. 1.

*Hepatic Fibrosis and Cirrhosis in Man in Relation to Malnutrition. John Higginson, B. G. Grobbelaar, and A. R. P. Walker.—p. 29.

* Studies on the Nature of Fibrinoid in the Collagen Diseases. David Gitlin, John M. Craig, and Charles A. Janeway.—p. 55.

Studies of the Effect of the Generalized Shwartzman Reaction on the Lesions of Experimental Allergic Encephalomyelitis. Byron H. Waksman and Raymond D. Adams.—p. 131.

Hepatic Fibrosis and Cirrhosis in Man in Relation to Malnutrition.—Over 1000 necropsy and surgical liver specimens from Bantu patients in South Africa were examined and classified as to the degree of portal fibrosis, the presence of cirrhosis, the presence of necrosis, and the degree of fatty infiltration. Diffuse portal fibrosis, varying from slight to severe, was present usually in the second half of life and usually in association with hemosiderin deposition. Severe cirrhosis occurred without relation to age and appeared to have resulted from postnecrotic scarring; regenerative nodular hyperplasia was present, and in approximately half the cases there was an associated hepatic carcinoma. Severe fatty disease was restricted to childhood and did not appear to be followed by necrosis and fibrosis. Although liver disease in

the Bantu adult did not appear to be the direct result of kwashiorkor in childhood, the data were interpreted to indicate a relationship between functional liver damage, resulting from malnutrition, and a postulated susceptibility in adult life to hepatotoxic factors, such as viruses, siderosis, and possibly drugs.

Studies on the Nature of Fibrinoid in the Collagen Diseases.—The Coons-Kaplan fluorescent antibody technique, employing rabbit antihuman fibrin antisera, was utilized on tissues in cases of rheumatoid arthritis, disseminated lupus erythematosus, dermatomyositis, subacute and chronic glomerulonephritis, and periarteritis nodosa and on cardiac auricular appendages in cases of rheumatic heart disease. Comparable sections were also stained with dyes customarily used for the demonstration of fibrin. Specific fluorescence with the antibody method was observed in areas of "fibrinoid" deposition, even in the absence of staining by the usual tinctorial methods, indicating that fibrinoid material is, at least in part, fibrinous.

American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Springfield, Ill.

76, Sept., 1956

This journal is recommended to all pediatricians, as it is a half-centennial issue devoted to the advances of radiology as related to pediatrics since the inception of radiology in 1896.

* The First Sixty Years of Pediatric Roentgenology in the United States, 1896 to 1956. John Caffey.—p. 437.
* Roentgenographic Investigation of the Human Skeleton During Early Fetal Life. Ronan O'Rahilly and David B. Meyer.—p. 455.
* A Significant Variant in the Ossification Centers of the Vertebral Bodies. Jonathan Cohen, Guido Currarino, and Edward B. D. Neuhauser.—p. 469.
* The Width of the Spinal Canal in the Growing Vertebra with Special Reference to the Sacrum: Maximum Interpediculate Distances in Adults and Children. Gerhart S. Schwarz.—p. 476.
* Observations on the Association Between Nutritive Failure, Skeletal Maturation Rate and Radiopaque Transverse Lines in the Distal End of the Radius in Children. Samuel Dreizen, Catherine Currie, Ellie Jo Gilley, and Tom D. Spies.—p. 482.
* The Ischiopubic Synchondrosis in Healthy Children: Some Normal Roentgenologic Findings. John Caffey and Steven E. Ross.—p. 488.
* The Skull in Childhood Myxedema: Its Roentgen Appearance. M. Arias Bellini and Ilda Neves.—p. 495.
* Prenatal Obstruction of the Fourth Ventricle. Donald D. Matson.—p. 499.
* Cytomegalic Inclusion Disease with Calcification Outlining the Cerebral Ventricles. George L. Sackett Jr. and Mary M. Ford.—p. 512.
* Congenital Cystic Adenomatoid Malformation of the Lung in Infants. John M. Craig, John Kirkpatrick, and Edward B. D. Neuhauser.—p. 516.

The First Sixty Years of Pediatric Roentgenology in the United States 1896 to 1956.—This article is of interest to radiologists, to pediatricians, or to any student of the history of medicine. It is particularly interesting as this history of pediatric roentgenology is presented by the physician whose name is synonomous with pediatric roentgenology in this country.

Some of the remarkable things mentioned are recorded below. To appreciate these facts we must recall that the discovery of x-rays by Roentgen was disclosed in 1896. 1. In 1897 two articles had appeared: (a) congenital dislocation of the hip, by Hoffa, and (b) the skeleton in cretinism, by Hoffmeer. 2. In 1897 a roentgen department for infants and children had been established in Graz, Austria. 3. In 1899 Boston Children's Hospital established a pediatric x-ray department. 4. In 1911 Harvard offered an elective course in pediatric roentgenology to its medical students.

These are but a few of the fascinating facts recorded, and some of the most historically significant discoveries as related to various organ systems are stressed.

Roentgenographic Investigation of the Human Skeleton During Early Fetal Life.—The roentgenographic method is one method of studying the skeleton during early fetal life. Serial sectioning and cleaving with or without staining are the other two methods. The method used in this study was to immerse the fetus in a 13.5% solution of silver nitrate to impregnate bones with silver salts. The authors discuss development of the extremities, ribs, sternum, vertebrae, and the component bones of the skull in some detail, offering charts and radiographs illustrating ossific centers.

A Significant Variant in the Ossification Centers of the Vertebral Bodies.—A curious variation in the ossification pattern of vertebrae is frequently noted in infants of the

newborn period. It consists of a longitudinal band of radiolucency seen on the lateral projection. A study of 17 of these cases found radiographically and then three studied histologically is included. A cartilagenous plate of hyaline type was found to correspond to the radiolucent area.

The theories of ossification of vertebral bodies are discussed. It appears from this study that about 5% have a double or dorsoventral ossification center, and this appears to be a transient stage of the development process. It seems probable that the notochord plays some part in dorsoventral doubling. The pattern seems significant, as it is seen three times more often in babies with congenital anomalies than in those without an anomaly.

The Width of the Spinal Canal in the Growing Vertebra with Special Reference to the Sacrum: Maximum Interpediculate Distances in Adults and Children.—The measurement of interpedicular distance has been well worked out in adults in the past. Previous studies on children have also been carried out, but none have included the sacrum and only one included the cervical spine.

This study demonstrates the different rate of growth of different portions of the spine. The spine continues to "grow" until age 18 to 25, at which time growth ceases.

The curves are presented and may be used by the "absolute" method of comparison of the interpedicular distance of one vertebral body or the "relative" method, by which several vertebrae are measured and the patient's "curve" is compared to the established normal. This method is apparently more satisfactory in that it offers an answer in earlier cases and even where absolute methods may be below maximum for the patient's age.

Observations on the Association Between Nutritive Failure, Skeletal Maturation Rate and Radiopaque Transverse Lines in the Distal End of the Radius in Children.—Radiopaque transverse lines or scars are frequently observed in the distal ends of the diaphysis of the radius in studies of normal children. Children vary in their susceptibility to bone scar formation, and multiple causes have been incriminated. This study was carried out to determine whether the speed of skeletal maturation and nutritional status are primary factors predisposing to bone scars.

Of 235 children studied, 134 had clinical and dietary evidence of nutritive failure and 103 had no past or present evidence of nutritive failure. All but four had evidence of radiopaque lines in the distal end of the radius.

The frequency of scarring was similar in both groups. While transverse lines are believed to be formed during periods of disturbed bone metabolism productive of either accelerated or arrested bone growth, the present study indicates that nutritional status per se is not the determining factor in susceptibility to bone scar formation in growing children. However, it does appear to play a role in the rapidity with which children recover from metabolic disturbances productive of bone scars.

Both fast- and slow-growing children are affected to the same degree, and rate of skeletal maturation is not of itself a primary predisposing factor in bone scar formation.

The Ischiopubic Synchondrosis in Healthy Children: Some Normal Roentgenologic Findings.—This article deals with an estimate of the disappearance time of the ischiopubic synchondrosis and the incidence of the combination of swelling and uneven mineralization of this synchondrosis in healthy children. Such swelling and irregular mineralization has been interpreted as a sign of juvenile osteochondrosis in Van Neck's ischemic necrosis. This study suggests that such swelling and uneven mineralization is an extremely common finding in normal children and constitutes a normal variant which at some ages (6-10 years) is present in the majority of children. The age of fusion varied so greatly that an average age of fusion was not arrived at. At 12 years 93% showed bilateral fusion.

The Skull in Childhood Myxedema: Its Roentgen Appearance.—The author lists a number of features in the skull which he feels are characteristic of childhood myxedema.

1. These are the craniofacial changes: small face with increased transverse diameter, flat forehead, short nose, widely separated eyes, flat palate, and prognathism.

2. Absence or delayed appearance of the cranial sinuses. This is an important sign and may help to differentiate congenital from acquired myxedema which occurs after 5½ years of life. There is scarce pneumatization of the mastoid air cells. When a thin diploe and well-developed sinuses are observed in a myxedematous patient the possibility of association with prehypophyseal endocrinopathy should be considered.

3. The sutures and synchondrosis reveal delayed closure, and there is shortening of the base of the skull.

4. The digital impressions are generally pronounced.

5. The sella turcica is enlarged, but its contour is sharp. It is round-shaped; the clivus is thick and vertical, and the posterior clinoids are not visualized. The greater wings of the sphenoid are thick and dense.

6. Dentition is delayed, especially is there delay of dental buds.

Prenatal Obstruction of the Fourth Ventricle.—Congenital atresia of the fourth ventricle foramina should be suspected clinically and can be confirmed radiographically in the first few weeks of life, as surgical treatment is feasible in this age group and end-results appear to be better the sooner definite treatment is instituted. Antemortem diagnosis of this condition was not commonly made prior to 1953.

The cases appear similar. A huge cyst-like structure is present in a much-enlarged posterior fossa. This is the enlarged fourth ventricle, which expands posteriorily and laterally and also projects downward into the cervical spinal canal. Anatomically the cisterna magna is obliterated or underdeveloped. The midline structures of the cerebellum are deficient or entirely absent. The cerebellar hemispheres are displaced laterally, and the flocculus appears rudimentary. The pons medulla and upper cervical cord are flat, broad, and displaced anteriorily. The tentoriaem and torcula are displaced upward. There is symmetrical internal hydrocephalus involving aqueduct of Sylvius and third and lateral ventricles. The embryological error producing this is not definitely understood. Obstruction is never complete, and tracer media may pass from the lateral ventricle to the lumbar subarachnoid space whereas air may not.

The clinical appearance is characteristic. There is enlargement of the head; symptoms and signs of increased intracranial pressure may or may not be present. The only neurological deficit is that due to internal hydrocephalus. The occipital region of the skull is very prominent, in contrast to cases with the other common cause of congenital hydrocephalism, stenosis of the aqueduct, where the posterior fossa and contents are small and the head is enlarged in the frontal and parietal regions.

The surgical treatment consists of suboccipital craniotomy and excision of the cyst wall as far as possible. The arch of the atlas must be removed so that the projection of the cyst into the cervical spinal canal can be excised. Hemostasis is an absolute necessity, as postoperative adhesions will cause recurrent obstructions to spinal fluid circulation.

This operation alone may be inadequate, as it was in four of the reported eight cases, possibly owing to the fact that simple removal of the primary obstruction is insufficient to restore normal intracranial pressure. The reason given is that since the surface subarachnoid pathways have never had a normal quantity of spinal fluid reaching them on the usual route they have never grown adequately and remain as atrophic, underdeveloped, potential spaces which fail to receive and pass along the fluid directed to them by surgery. Here a further shunting procedure may be necessary for satisfactory relief of increased intracranial pressure.

Cytomegalic Inclusion Disease with Calcification Outlining the Cerebral Ventricles.—A case of inclusion-body disease is reported in a newborn infant with demonstration of a line of calcification outlining the lateral ventricles. A similar finding has been reported once previously.

Sixty-six cases of cytomegalic inclusion disease have been reported in the literature previously. It may occur in stillborn infants, and infants dying under 2 months of age, in whom no other cause of death can be found. It seems uniformly fatal, and no specific therapy is known. This case is added because of the unusual radiographic finding of calcification outlining the lateral ventricles. Additional findings in this case included microcephaly, overriding of the bones of the calvarium, moderate hepatic and splenic enlargement, jaundice, progressive anemia, and petechiae.

The antemortum diagnosis may be made by finding large numbers of epithelial cells in the urine, which should have intracytoplasmic inclusions and perhaps some specific nuclear inclusions.

Congenital Cystic Adenomatoid Malformation of the Lung in Infants.—Four cases of cystic malformations of the lung are reported in which surgery was performed in the first two weeks of life. These cases have features identical to those of a condition described in one case previously by Ch'in and Tang as congenital adenomatoid malformation of the lung.

The four cases presented similar histories and physical signs. They had cyanosis, rapid respiration, and an absence of respiratory distress or fever. Examination revealed displacement of the mediastinum away from the side of the affected lung, fullness to percussion, and diminished breath sounds over the affected lung.

Radiographically in all four cases the signs were those of an intrapulmonary mass containing scattered radiolucent areas, irregular in size and shape. Outlines of the mass were sharp, and the malformation was limited to one lobe. The heart and mediastinum were displaced to the opposite side, and the affected lung frequently showed evidence of herniation across the midline.

Pathologically there is a lack of the usual separation into discrete lobules. This correlates with a lack of a well-defined intrapulmonary bronchial system, and there is an absence of a normally formed bronchus supplying the mass. There is a lack of cartilage supporting structures. The adenomatous hyperplasia of the lung structure is seen in the relative increase in the terminal bronchiolar structures as well as in occasional polypoid arrangements of the mucosa.

Surgery is felt to be mandatory in this condition, as in two of the cases the involved lungs rapidly increased in size, further compromising respiratory function. Three of the four cases subjected to surgery are reportedly doing well. The fourth died shortly after surgery.

Annals of Internal Medicine, Lancaster, Pa.

45, No. 1 (July) 1956

The Interrelationships Between Addison's Disease and Active Tuberculosis: A Review of 125 Cases of Addison's Disease. J. P. Sanford and C. B. Favour.—p. 56.

Idiopathic Pericarditis. E. A. Stewart Reid, J. Lawrence Hutchison, John D. E. Price, and Robert L. Smith.—p. 88.

*Recent Advances in the Laboratory Diagnosis of Virus Infections. A. J. Rhodes.—p. 106.

Acute Rheumatic Fever in a Large Southern Hospital over the Five Year Period 1950 Through 1954. Samuel L. Lieber and Joe E. Holoubek.—p. 118.

Case Report: Chronic Meningococcemia. Maurice Gore.—p. 142.

Editorial: Epidemiology of Sarcoidosis. Max. Michael Jr.—p. 151.

45, No. 2 (Aug.) 1956

*Systemic Lupus Erythematosus: Recent Advances in Its Diagnosis and Treatment. Edmund L. Dubois.—p. 163.

Modern Treatment of the Malabsorption Syndrome in Adults. John M. Finlay and Keith J. R. Wightman.—p. 191.

45, No. 6 (Dec.) 1956

Streptococcal Bacteremia Without Endocarditis: Clinical Observations. Alexander Shirger, William J. Martin, and Donald R. Nichols.—p. 1001.

Klebsiella in Respiratory Disease. William Weiss, George M. Eisenberg, Alfred Spivack, Jay Nadel, Harold L. Kayser, Siri Sathavara, and Harrison F. Flippin.—p. 1010.

* A New Concept of Familial Adenomatosis. Roy C. Gumpel and Jose D. Carballo.—p. 1045.

Rheumatism and Arthritis: Review of American and English Literature of Recent Years (Eleventh Rheumatism Review): Part II. William D. Robinson, Joseph J. Bunim, William S. Clark, Darrell C. Crain, Ephraim P. Engleman, Donald C. Graham, Max M. Montgomery, Bernard M. Norcross, Charles Ragan, Marian W. Ropes, Edward F. Rosenberg, and Charley J. Smyth.—p. 1059.

Recent Advances in the Laboratory Diagnosis of Virus Infections.—Faster and less expensive methods are or soon should be available in all large hospitals. Examination of epithelial scrapings and innoculation of suckling mice are used for certain purposes, but the most valuable advance has been in simplifying tissue culture methods by the use of synthetic nutrient media, the recognition of the cytopathogenic effect (microscopically visible changes caused by the growth of virus), and inhibition of the cytopathogenic effect by immune serum.

In poliomyelitis, the virus may be cultured from stools or throat swabs in monkey kidney or human tissue cultures in about 90% of paralytic cases. The virological diagnosis may require as little as three to four days. It is especially useful in differentiating those cases clinically indistinguishable from paralytic and nonparalytic poliomyelitis which are actually caused by "orphan" or "echo" virus and Coxsackie viruses. Neutralization and complement-fixation tests on the patient's serum can also be carried out in tissue cultures.

In cases of aseptic meningitis innoculation of monkey kidney cultures with throat washings, stool, or spinal fluid can be used for the identification of poliomyelitis virus, Group B Coxsackie viruses, and "orphan" virus. Group B Coxsackie viruses may also be identified in epidemic pleurodynia in the same manner. In herpangina throat swab or stool material is injected into suckling mice, since the etiologic agents, Group A Coxsackie viruses, do not usually grow in tissue cultures. In pharyngoconjunctival fever and some cases of epidemic keratoconjunctivitis APC viruses can be isolated in HeLa cell cultures, in which they produce characteristic degenerative changes.

An etiological diagnosis can be obtained in vesicular skin eruptions due to herpes simplex, herpes zoster, vaccinia, variola, and varicella by examination of scrapings from the base of a lesion. In herpes simplex, herpes zoster, and varicella, but not in smallpox and vaccinia, multinucleated giant cells with intranuclear inclusion bodies are seen on smears. In tissue cultures of rabbit corneal epithelium cytopathogenic changes, giant cells, and nuclear inclusions bodies are produced by herpes simplex virus, whereas vaccinia produces cytopathogenic changes and cytoplasmic inclusions and the viruses of herpes zoster and varicella do not grow.

Systemic Lupus Erythematosus: Recent Advances in Its Diagnosis and Treatment.—This diagnosis has been made four times more frequently at the Los Angeles County General Hospital since the introduction of the L. E.-cell tests, beginning in 1950. There are now four types of test: one using heparinized blood, one using clotted blood, the Snapper ring test, and one using glass beads to traumatize the leukocytes. They vary considerably in sensitivity, but, since any one may be positive when the others are negative in an individual case, a battery of tests should always be performed. By repeated testing, positive results were obtained in 74% of 163 patients, including 58 in the first two decades of life, with disseminated lupus, and typical L. E. cells were found only in this disease and possibly the hydralazine syndrome.

Salicylates and bed rest may be adequate treatment for mild cases, but if they fail or if cutaneous lesions are present, antimalarial drugs should be given. Atabrine, chloroquine, and amodiaquin have a nonspecific anti-inflammatory action as well as an almost specific effect on the skin lesions of discoid and disseminated lupus. A total of 21 of 27 patients on atabrine, 12 of 14 on chloroquine, and 12 of 15 on amodiaquin were benefited, with improvement of joint symptoms in a few days and disappearance of skin lesions in a matter of weeks. Because large doses were used in this study, there was a high incidence of disturbing side-effects. When antimalarial therapy fails or the patient is critically ill, steroid hormones should be used in doses sufficient to produce symptomatic improvement and abolish fever. High dosage should be maintained until all abnormal physical findings have improved and anemia is corrected; then the dose should be decreased. There were 107 of 119 patients treated with adequate doses who had at least temporary benefit, and 49 had full remission so that hormones could be discontinued. In those patients requiring maintenance steroid therapy, tapering the dose was often facilitated by the addition of antimalarial drugs. When nephrotic manifestations are present and the patient is still edematous after about two months' treatment with antimalarial drugs or hormones, nitrogen mustard is indicated; 13 of 16 edematous nephrotics were improved by the use of this agent.

The two chief causes of death in this series were progressive renal failure (33%) and cerebral arteritis (43%). The frequency of spontaneous remissions (39% in this series) and the lack of a comparable control series makes evaluation of treatment difficult. However, of a group of 59 untreated or inadequately treated cases 50% were dead after 2 years, whereas of 138 adequately treated patients, ill for 24 months or more, less than 10% have died.

A New Concept of Familial Adenomatosis.—This disease is characterized by multiple adenomatous polyps of the colon, appearing in adolescence and early adulthood, with a very high incidence of malignant change, occurring in families as a Mendelian dominant trait. These features place a grave responsibility on the physician, not only to recognize cases but also to investigate the families of affected patients.

By the time the symptoms of polyposis, diarrhea, passage of blood and mucus, and attacks of cramp-like abdominal pain have brought the patient to the doctor, cancer is present in 40% of cases. However, the development of polyposis may be suspected or anticipated and appropriate studies carried out when the patient or members of the family have multiple

exostoses, epidermoid cysts, and other benign and malignant tumors of connective tissue; for there is evidence from several published case reports and the three cases reported here that there is a close association between such lesions and adenomatosis of the colon. Perhaps both are caused by mutation of the same pleiotropic gene, or perhaps they are fortuitously occurring congenital anomalies due to multiple mutations of distinct genes. Furthermore, these tumors are often present from childhood and are therefore detected long before the bowel lesions are present. In patients with the surface tumors polyposis should be expected even though it is not yet present. In a few instances familial adenomatosis of the colon has been reported in childhood—four times in children under 2 and once in a 15-year-old boy. Colectomy is indicated for the prevention of cancer, even in the premalignant phase.

Archiv für Kinderheilkunde, Stuttgart

154, No. 1, 1956

Contibution to the Etiology of Perthes Disease. Helene Tietz.—p. 6.
*Some Special Features of Phonocardiography. E. Ziehme.—p. 14.
Alkaline Serum Phosphatase in the Maternal and Fetal Blood After Vitamin D Doses in Late Pregnancy. W. Jung and G. Stark.—p. 23.
Wolff-Parkinson-White Syndrome in Childhood. D. Knorr.—p. 28.
Some Peculiarities of Coagulation Factors in Treated and Untreated Cases of Pertussis. Fr. Koch, H. E. Schultze, and G. Schwick.—p. 39.
The X-Ray and Clinical Significance of Mediastinal Hernias in Childhood. H. Schäfer.—p. 47.

154, No. 2, 1956

Peritonitis After Intestinal Perforation in the Neonatal and Infant Period. E. Knopf.—p. 111.
Idiopathic Megacolon and Its Treatment. F. Rehbein and W. Hüther.—p. 126.
Unusual Religious Movements Among Children and Adolescents. P. Habermann.—p. 138.
Serological Differential Diagnosis of Congenital Syphilis and Placental Transfer of Maternal Reagents. F. Müller.—p. 153.
Rare Forms of Ileus in the Neonatal and Infantile Period. W. Ch. Hecker and H. Berg.—p. 162.

154, No. 3, 1957

The Child in the Hospital. J. Ströder and E. Geisler.—p. 216.
*On the Temperature Regulation of Prematures, Under Special Consideration of the Controversy on Warm or Cold Treatment. H. W. Kintzel.—p. 238.
The Application of Acid Milks in Infant Nutrition. W. Feldheim.—p. 247.
*Giant Cells in Nasal Secretion During Measles Prodromi. K. Haneke.—p. 253.
Herpetiform Dermatitis in Early Childhood. F. Küster and D. Salus.—p. 257.
Postvaccinal Diabetes Insipidus. H. Rodeck.—p. 265.

Some Special Features of Phonocardiography.—In young infants the first sound occurs earlier and is shorter. The younger the child, the shorter the second sound. In healthy children auricular sounds or presystolic vibrations are often encountered that are not perceptible to the ear.

On the Temperature Regulation of Prematures, Under Special Consideration of the Controversy on Warm or Cold Treatment.—Different situations of prematures in regard to the functional inability of heat regulation are discussed. Special consideration is paid to the temperature on admission. If they are admitted cool, it is advisable to keep prematures up to a weight of 2000 gm. at first at a low temperature. In prematures of higher weight, this procedure is inadvisable.

Giant Cells in Nasal Secretion During Measles Prodromi.—The nasal discharge of 16 children was cytologically examined during the prodromal stage of measles. In 15 cases epithelial giant cells were found. They may be of specific diagnostic significance, since they were not detectable in control series of other catarrhal secretions.

Blood, New York

11, No. 11 (Nov.) 1956

*Thrombocytoasthenia and Thrombocytopathia—Old Names and New Diseases. H. Braunsteiner and F. Pakesch.—p. 965.

Studies on Spontaneous in Vitro Autohemolysis in Hemolytic Disorders. Lawrence E. Young, Mary Jane Izzo, Kurt I. Altman, and Scott N. Swisher.—p. 977.
The Detection and Estimation of Fetal Hemoglobin by Means of the Alkali Denaturation Test. J. H. P. Jonxis and T. H. J. Huisman.—p. 1009.
The Direct Coombs Test in Lead Poisoning. Donald A. Sutherland and Anna M. Eisentraut.—p. 1024.
Editorial: Etiology of Leukemia: A Case for the Virus Theory. Steven O. Schwartz.—p. 1045.

11, No. 12 (Dec.) 1956

The Hemostatic Defect of Uremia: I. Clinical Investigation of Three Patients with Acute Post-Traumatic Renal Insufficiency. Camilo Larrain and Edward Adelson.—p. 1059.
The Hemostatic Defect of Uremia: II. Investigation of Dogs with Experimentally Produced Acute Urinary Retention. Camilo Larrain and Robert D. Langdell.—p. 1067.
Bleeding Tendency in Uremia. Jessica H. Lewis, Marjorie B. Zucker, and John H. Ferguson.—p. 1073.
*Immunologic Features of Erythrocyte Sensitization: I. Acquired Hemolytic Disease. John H. Vaughan.—p. 1085.
A Summary of Atypical Antibodies, Rare Genotypes, and ABO Hemolytic Disease, Encountered in a One Year Survey. Philip Levine, Elizabeth Robinson, Marjory Stroup, Robert McGee, and Louella N. Bushnell.—p. 1097.
*Studies on the Pathogenesis of Splenic Anemia. E. R. Giblett, A. G. Motulsky, F. Cassrd, B. Houghton, and C. A. Finch.—p. 1118.

Thrombocytoasthenia and Thrombocytopathia—Old Names and New Diseases.—An analysis based on study of 23 patients with qualitative platelet defects was made with an attempt at classification of such disorders. A uniform clinical picture was found which was characterized by severe bleeding, including hemarthroses in 3. In all the bleeding time was prolonged. Platelet counts and plasma coagulation factors were normal.

Five patients were classified as having thrombocytoasthenia, a disease attributed to defective platelet pseudopod formation and lack of spreading of platelets. The defect was found to persist whether the platelets were in pathologic or normal plasma, serum, heated serum, or barium-adsorbed serum. However, in saline or plasma substitutes the platelets behaved normally. Clot retraction was manifestly disturbed, or latent disturbance could be detected by thrombelastography. Serotonin did not correct the defect. Thromboplastin generation and prothrombin consumption were normal.

The 18 remaining cases were classified as thrombocytopathias. These presented a less uniform picture and were divided into three subgroups. In the first group there was a decrease in the thromboplastic activity of platelets and platelets were isolated on smear and some cases showed morphologic anomalies. A group in which the thromboplastic activity of platelets, as evidenced by thromboplastin generation and prothrombin consumption, was only temporarily pathologic, was termed "probable thrombocytopathias." In the third subgroup no evidence of decreased thromboplastic activity of platelets could be detected by present methods, despite the evident bleeding. These were termed "possible thrombocytopathias." Capillary microscopy in all three groups was normal.

Immunologic Features of Erythrocyte Sensitization: I. Acquired Hemolytic Disease.—It has been generally held that the material rendering red cells susceptible to the Coombs' test is γ-globulin. Recent studies indicate that in acquired hemolytic disease red cell sensitization may be due, in some cases, to globulin other than γ-globulin. By use of specifically absorbed Coombs' sera the author shows that cell sensitization in acquired hemolytic disease may be due to γ-globulin or to non-γ-globulin serum components. The latter may be either warm-reacting or cold-reacting (cold agglutinin).

Studies on the Pathogenesis of Splenic Anemia.—Experimental hypersplenism was produced in rats, with use of methylcellulose. These rats, as well as normal and splenectomized rats, were studied to determine the role of a large spleen in the production of anemia. In the rats treated by intraperitoneal methylcellulose injection anemia became evident. There was a marked decrease in red cell life-span, reticulocytosis, and marrow erythropoietic hyperplasia, indicating erythrocyte destruction with compensatory production. It was further shown that injected cells were taken up by the hypertrophied spleen and splenectomy reversed the hemolytic process, indicating that the enlarged spleen was the major cause and site of red cell destruction.

Methylcellulose when injected into splenectomized rats did not produce anemia. There was no evidence of a depressant effect of the spleen on the marrow. Nor was there evidence of an autoimmune mechanism for the anemia. It is postulated that the mechanism for red

cell destruction by the methylcellulose-treated spleen is a combination of sequestration and stasis of erythrocytes in the enlarged pulp compartment plus erythrocyte phagocytosis. This study may serve as a model for investigation of "hyperfunctional spleen" in human disease.

Boletín médico del Hospital infantil, México, D. F.

13, No. 4 (July-Aug.) 1956

Physiopathology of the Salmonellas: IV. Regeneration of Serial Cholinesterase in Children During Active and Convalescent Typhoid. Jesus Kumate, Lazoro Benevides, Berta Lelo de Larrea, and Luis Rangel.—p. 777.

Infectious Diarrhea Mortality in Hospitalized Children Under 2 Years of Age. Joaquin A. de la Torre.—p. 785.

Renal Function Evaluation by Means of Inulin and Sodium-Para-Amino Hippurate Clearance and Saturation Tests in Normal Children. Rapheal Soto Allande and others.—p. 793.

Dehydration in the Malnourished Child. Dr. Gustavo Gordillo P. and Jorge Cortes R.—p. 803.

Clinical Cases:

(a) Bronchogenic Cysts of the Mediastinum. Carlos Sarinana, A. Torres de Anda, and Humberto Caldero.—p. 813.

(b) A Case of Chondrodystrophy Calcificans Congenita. Marcilino Figuervac and Luis Rangel R.—p. 819.

13, No. 5 (Sept.-Oct.) 1956

Editorial: The Teaching of Pediatrics in Medical Programs. Federico Gomez.—p. 861.

Studies in the Undernourished Infant: XVIII. Calcium, Inorganic Phosphorus and Alkaline Phosphatase Serum Levels in Preschool Children with Chronic Malnutrition and in the Course of Their Recovery. Federico Gomez and others.—p. 865.

Problems of Respiration in the Premature Infant: Blood Oxygen Determination; Normal Values. Alvarez de los Cobos, E. Jurado Garcia, G. Sagaon Ramirez, and E. Leon Villalba.—p. 875.

Morphology of the Thyroid Gland in Undernourished Children. Kurt Ambrosius.—p. 897.

New Type of Salmonella Organism—Salmonella Azteca. J. Olarte, P. P. Edwards, Alma C. McWhorten, and J. J. A. de la Torre.—p. 907.

*Clinical Cases:

(a) Dermoid Tumors of the Nervous System. Luis Duran Romano, Marin Ramos Contreras, and Miguel Ramos Murgina.—p. 913.

Dermoid Tumors of the Nervous System.—Because of the rarity of dermoid tumors of the nervous system in childhood, the authors present two cases which were diagnosed and successfully removed at the Childrens Hospital in México, D. F.

These tumors are due to a defect in embryonic development between the third and fifth weeks of embryonic life, when the neural ectoderm separates from the epithelial ectoderm. Although it is possible for groups of epithelial cells to be left in the neural tissue at any portion of the nervous system, it is easy to explain the greater frequency of such defects in the sacral and suboccipital regions.

One case was that of a 4-year-old boy who suffered headaches of great intensity, vertigo, nausea, vomiting, and ataxic gait. The physical examination revealed the circumference of the head to be 52 cm., and the "cracked pot" sign was present. The other signs were characteristic of a lesion which was expanding. Excellent ventriculograms are included which demonstrated dilatation of the lateral ventricles, and preoperation diagnosis was medulloblastoma displacement of the fourth ventricle. Surgical procedures are described. The tumor was removed completely and was full of various epithelial derivatives such as sebaceous material and hairs 13 cm. in length. The recovery was uneventful, and the child has no sequelae.

The second case was that of a 9-year-old girl who had lumbosacral pain dating from a fall in the sitting position at the age of 6 years. There was intense pain and a peculiar gait in which she held her right extremity flexed at the knee and abducted, bearing most of her weight on the left leg.

A flat plate of the spinal column showed displacement of the vertebrae from the 11th dorsal to the 2nd lumbar. Diagnosis of intramedullary dermoid tumor was made. There was a successful removal. Surgical details are described. The tumor was dermoid. The patient had some paraesthesia and incontinence of the bladder following the operation which persisted for some time after her discharge from the hospital.

Bulletin of The Johns Hopkins Hospital, Baltimore

99, No. 5 (Nov.) 1956

Some Physico-Chemical Aspects of Calcification in Vitro. William C. Thomas et al.—p. 287.

99, No. 6 (Dec.) 1956

Some Problems Relating to Staphylococcal Infections: A Comparison of Mouse-Virulence with Other Properties. A. Murray Fisher and Barbara W. Thompson.—p. 341.

* A Mechanism of Bradycardia in the Fetal Lamb in Utero. William M. Paul.—p. 357.

A Mechanism of Bradycardia in the Fetal Lamb in Utero.—The purpose of this study was to observe the effect of uterine contraction on fetal heart rate and maternal and fetal blood oxygen saturation. Gravid ewes near term were used as the experimental animals. Uterine (maternal) and umbilical (fetal) veins were catheterized; a catheter, inserted and fixed in the amniotic sac, was attached to a water manometer, and the fetal heart rate was recorded by direct auscultation on the uterus. After base-line observations Pitocin was injected intravenously to produce uterine contractions and the effects on maternal and fetal oxygen saturation, amniotic pressure, and fetal heart rate were observed.

Uterine contraction caused a fall in maternal and fetal oxygen saturation and fetal bradycardia. The strength of contraction appears to be related to oxygen desaturation in a straight-line relationship. On the other hand, a critical level of oxygen saturation (10% or less in all but one of the animals observed) appears to be necessary before bradycardia occurs and this, therefore, is evidence of profound hypoxia.

Canadian Medical Association Journal, Toronto

75, Nov. 15, 1956

* Cervical Lymphadenitis in Children Caused by Chromogenic Mycobacteria. F. H. Prissick and A. M. Mason.—p. 798.

* Neonatal Hepatitis. D. L. Collins.—p. 828.

Appendicitis in Infancy. W. Dutz and S. Hanson.—p. 832.

Congenital Anomalies of the Digestive Tract: Report of 2 Cases. J. M. Chamberland, R. Fortin, and J. Lavoie.—p. 837.

75, Dec. 15, 1956

* Observations on Neonatal Mortality. D. H. Bowden, A. M. Goodfellow, and C. E. Snelling.—p. 1000.

76, Jan. 1, 1957

Closure of Interauricular Septal Defects Under Hypothermia. J. A. Gravel.—p. 27.

76, Jan. 15, 1957

* The Complete Elimination of Retrolental Fibroplasia. P. Banister and J. C. Locke.—p. 81.

* Some Problems in Pediatric Gynecology. F. E. Bryans.—p. 150.

Cervical Lymphadenitis in Children Caused by Chromogenic Mycobacteria.—The present communication describes the source, morphology, and staining reactions and the cultural, biochemical, and pathogenic characters of 14 strains of chromogenic acid-alcohol-fast rods isolated from pathological specimens from human infections suspected of being tuberculous in nature.

Ten of the strains were isolated from suppurating facial, submaxillary, or cervical lymph nodes in children. All were closed lesions. Two strains were isolated from empyema; one, from a bronchial aspiration fluid, and one, from tissue of a knee joint proven to be tuberculous.

Brief histories of 10 children are given, and abstracts are presented of the 4 cases where organisms were obtained other than from a cervical lymph node. The lesion in the lymph nodes could not be differentiated from the lesion of tuberculosis.

The morphology and staining properties of the organisms are given. There is a discussion of the cultural and biological characters of the organisms in relation to Mycobacterium ulcerans, Mycobacterium balnei, etc.

The course of the disease in the 10 children was benign, and healing occurred slowly without any sinus formation. Studies of the tuberculin test were made in most cases.

The strains of organism produced were inoculated into guinea pigs, hamsters, rats, and hens. Localized lesions were consistently produced in guinea pigs inoculated intraperitoneally with the strains isolated from the cervical lymph nodes, but generalized lesions were rarely observed. Localized lesions were occasionally found in rats and hamsters.

The authors suggest the term Mycobacterium scrofulaceum for the species of organism which they isolated from the subacute lymph node infections in children.

Neonatal Hepatitis: Including a Case Associated with Maternal Hepatitis During Pregnancy.—Neonatal hepatitis may simulate biliary duct atresia. It is important to differentiate the two conditions, because the mortality is greatly increased if abdominal exploration is done when hepatitis is present.

The author discusses the clinical picture and recognizes two types of viral hepatitis: (*a*) that due to infection from oral ingestion of virus and (*b*) homologous serum hepatitis. The evidence that neonatal hepatitis is due to a virus is given in detail, and two cases are reported, one in which both baby and mother died of acute viral hepatitis, probably of homologous serum type, and one in which biliary atresia was ruled out by laparotomy when the infant was 3 months old and in which the mother had no clinical evidence of hepatitis.

Observations on Neonatal Mortality.—The authors report the results of a 3-year study of neonatal mortality carried out at the Hospital for Sick Children, Toronto. Congenital anomalies occurred in 31% of 492 autopsies. Abnormal pulmonary ventilation and infections together form the largest group of cases in this series (43%).

Abnormal pulmonary ventilation was due to (*a*) pulmonary hyaline membrane formation (42%); (*b*) atelectasis (pulmonary immaturity)—number not noted; (*c*) massive pulmonary hemorrhage in 22 of the 492 autopsies; (*d*) aspiration of amniotic fluid—number not noted. (Presumably the totals will be given in a later report in a city-wide study.)

Pulmonary infections accounted for deaths of 64 babies. Infections must be regarded as preventable, and many of these deaths might have been avoided.

Prematurity is the most important single factor which influences neonatal mortality and morbidity. The causes of prematurity are unknown in 66% of cases, and it is in this field that major investigative work is required.

The Complete Elimination of Retrolental Fibroplasia.—In spite of advances in knowledge of the etiology of retrolental fibroplasia, cases continue to occur. The authors report a study which convinces them that this condition is entirely preventable and that all future cases must be assumed to be due to human or mechanical error.

Oxygen concentration was not permitted to exceed 40%, except in special cases, and oxygen concentrations were measured every two hours with a Beckman analyzer. Not 1 of 126 premature babies under observation showed even the mildest manifestations of active retrolental fibroplasia. Recommendations for the control of oxygen therapy in premature babies are outlined.

Some Problems in Pediatric Gynecology.—This is a review article and emphasizes many important points in both history-taking and physical examination, e. g., the upper vagina may be explored digitally or with a culture swab without serious discomfort. In very young children anesthesia is necessary. Visualization of the vault may be accomplished with a Kelly air cystoscope, an infant laryngoscope, or a small Sims speculum.

The embryology of the female genital tract is discussed in relation particularly to congenital anomalies. The physiological development with abnormalities is discussed also under the headings of precocious puberty, amenorrhea, menarche, dysmenorrhea, etc. Common gynecologic complaints are noted, and the usual infections are mentioned, with details of treatment. The authors state that explanation and reassurance are the most frequently employed forms of treatment.

Endocrinology, Springfield, Ill.

59, Sept., 1956

* Prevention of Severe Cardiovascular and Smooth Muscle Necrosis in the Rat by Thyro-Parathyroidectomy. David Lehr and Constance R. Matin.—p. 273.

* The Effect of Unilateral Adrenalectomy on Adrenal Venous 17-Hydroxycorticosteroid Output in the Dog. William F. Ganong and David M. Hume.—p. 302.
* The Relation of Succinate to Adrenocortical Function. Walter M. Booker, Frances DaCosta, Samuel W. Mitchell, and Marvin Skelton.—p. 317.
* Thyroxine Secretion in Rats Exposed to Cold. Richard Woods and L. D. Carlson.—p. 323.
* Effect of Glucagon on Glycogen in Rats and Rabbits. Mary A. Root.—p. 340.
* Aldosterone and Hydrocortisone Secretion by the Denervated Adrenal. Ronald Fleming and Gordon Farrell.—p. 360.

59, Oct., 1956

* The Effect of Ethyl Alcohol on Adrenal Cortical Activity in Mice. George A. Santisteban and Chester A. Swinyard.—p. 391.
* Influence of Adrenal Cortex on Gastric Pepsinogen in the Rat. Basil I. Hirschowitz, David H. P. Streeten, and H. Marvin Pollard.—p. 419.
* The Effect of Growth Hormone on Hematopoiesis in Hypophysectomized Adult Female Rats. Howard A. Meineke and Roger C. Crafts.—p. 444.
* Effect of Estrogen on the Metabolism of Protein-Bound Iodine. Joseph D. Feldman and T. S. Danowski.—p. 463.
* Loss of Appetite for Alcohol and Alcohol Beverages Produced in Rats by Treatment with Thyroid Preparations. Curt P. Richter.—p. 472.

59, Nov., 1956

* The Inhibition of Hypophysectomy-Induced Changes in the Rat Submaxillary Glands. William G. Shafer, Patricia G. Clark, and Joseph C. Muhler.—p. 516.
* Evidence for Diencephalic Regulation of Aldosterone Secretion. Elizabeth W. Rauschkolb and Gordon L. Farrell.—p. 526.
* Alterations in Chick Thyroid Function Induced by Cobalt. Joseph P. Friss, Francis S. Greenspan, William H. Carnes, and William Lew.—p. 555.
* Effect of Phosphate in Enhancing the Action of Triiodothyronine. Kathleen E. Roberts, George Firmat, John Prunier, Morton K. Schwartz, and Rulon W. Rawson.—p. 565.
* The Inhibitory Effect of Reserpine on ACTH Secretion in Response to Stressful Stimuli. Herbet Wells, F. Norman Briggs, and Paul L. Munson.—p. 571.

59, Dec., 1956

* Neurohypophysis and Water Metabolism in the Toad, Bufo Bufo (L.). C. Barker Jorgensen, K. G. Wingstrand, and Per Rosenkilde.—p. 601.
* Density as an Index of the Effects of Estrogens on Bone. Richard A. Edgren and David W. Calhoun.—p. 631.
* Effect of Testosterone on Circulating Eosinophils in the Guinea Pig. Malvina Schweizer.—p. 642.

60, Jan., 1957

* Thyroid in B-12 Deficient Chick Embryos. T. M. Ferguson, R. H. Rigdon, and J. R. Couch.—p. 13.
* The Gonadal Regulation of Cholesteremia in the Rat. Louis C. Fillios.—p. 22.
* The Influence of Vitamin B_{12} Deficiency on the Uptake of I^{131} by the Thyroid Gland in Adult and Embryonic Chickens. T. M. Ferguson, J. B. Trunnell, B. Dennis, P. Wade, and J. R. Couch.—p. 28.
* Studies on the Nature of the Thyroid-Pituitary Interrelationship. R. C. Goldberg, J. Wolff, and R. O. Greep.—p. 38.
* Changes in Bones and Joints of Underfed Mice Bearing Anterior Hypophyseal Grafts. Ruth Silberberg and Martin Silberberg.—p. 67.
* The Effects of Carbutamide (BZ-55) on Blood Sugar Levels of Depancreatized Dogs Given Insulin. I. B. Fritz, M. Weinstein, J. V. Morton, and R. Levine.—p. 76.
* The Effect of Furadroxyl Treatment and X-Irradiation on the Hyaluronidase Concentration of Rat Testis. E. Steinberger and Warren O. Nelson.—p. 105.

Prevention of Severe Cardiovascular and Smooth Muscle Necrosis in the Rat by Thyro-Parathyroidectomy.—In the course of studies on experimental arteriosclerosis in the albino rat, it was noted that inhibition of thyroid hormone production by propylthiouracil had a protective effect against the development of cardiovascular and smooth muscle necrosis as well as against secondary calcification following standard renal injury. In the present paper it is demonstrated that thyroparathyroidectomy provides clear-cut protection against the emergence of muscular necrosis and its sequelae.

The Effect of Unilateral Adrenalectomy on Adrenal Venous 17-Hydroxycorticosteroid Output in the Dog.—It has been assumed that the hypertrophied adrenal cortex is capable of a greater steroid output than the normal, but direct proof of this assumption has been lacking.

The present data show that there is a significant increase in the maximum 17-hydroxycorticosteroid output from the remaining adrenal gland one week after unilateral adrenalectomy. This is correlated with an increase in the weight of the gland and histologic evidence of adrenocortical hypertrophy.

The Relation of Succinate to Adrenocortical Function.—The probable relationship between succinate and adrenocortical function during stress has been suggested. The results of experiments reported here indicate that succinate is deleterious to the adaptation of animals to cold stress and that this effect may be antagonized by cortisone in the whole animal, both intact as well as adrenalectomized. The suggestion is offered that cortisone may act during stress to slow down the demand upon the metabolic reserve which succinate would seem to draw upon.

Thyroxine Secretion in Rats Exposed to Cold.—The importance of the thyroid hormone in the increased heat production necessary for survival in a cold environment has been established. The results of experiments reported here confirm the previous evidence that thyroxine secretion is greatly increased following two weeks at a low environment temperature. It is further established that thyroid activity remains at a high level throughout a 60-day cold exposure.

Effect of Glucagon on Glycogen in Rats and Rabbits.—The results of experiments with the chronic administration of glucagon in large doses to rats and rabbits show that this substance is capable of causing glyconeogenesis. The fact that the sensitivity of rabbits treated daily with glucagon is enhanced strengthens the suggestion that the status of liver glycogen stores determines the degree of hyperglycemia produced by a standard dose of glucagon.

Aldosterone and Hydrocortisone Secretion by the Denervated Adrenal.—It is concluded that the presence of the nerve supply to the adrenal probably plays no major role in the adrenal secretion of either steroid. The data are consistent with the view that the secretion of aldosterone is under the control of a circulating hormone.

The Effect of Ethyl Alcohol on Adrenal Cortical Activity in Mice.—It has been suggested that a hypofunction of the pituitary-adrenal system may be an important factor in the etiology of chronic alcoholism. In this study, the "thymo-regressive response" has been utilized to make qualitative and quantitative evaluations of the increase in adrenocortical activity associated with acute alcoholic intoxication. This was done by determining the amount of thymic atrophy which occurred in a group of intact mice given an intoxicating dose of ethyl alcohol and comparing this with the thymoregressive responses of groups of adrenalectomized mice receiving a similar dose of alcohol concurrent with one of a series of graded doses of Compound F acetate (17-hydroxycorticosterone acetate) and also with the thymic atrophy which occurred in adrenalectomized animals treated only with the graded doses of the hormone.

There was a twenty-five- to fiftyfold increase in corticoid activity associated with the alcohol treatment.

Influence of Adrenal Cortex on Gastric Pepsinogen in the Rat.—Hypophysectomy, adrenalectomy, and the administration of cortisone have been shown to cause changes in the pepsin content of the gastric juice of rats, which paralleled changes in the size and zymogen content of the chief cells of the gastric mucosa.

The results obtained in the experiments here reported have shown that, while various adrenocortical steroids will restore to normal the gastric pepsinogen depressed by adrenalectomy, none appeared capable of raising this content above normal. Corticotropin, however, did cause an increase in pepsinogen above normal.

The Effect of Growth Hormone on Hematopoiesis in Hypophysectomized Adult Female Rats.—The fact that hypophysectomy is followed by anemia is well established. The present investigation was undertaken in an attempt to add further details concerning the effect of growth hormone on hematopoiesis.

It was found that growth hormone therapy in hypophysectomized anemic rats produced a hyperplasia of the bone marrow, the erythroid elements responding in a more marked fashion than the myeloid elements; the changes were accompanied by an increase in reticulo-

cyte percentage. In spite of this growth of the marrow, the peripheral anemia was not altered; blood volume studies did not support the view that this lack of effect on the peripheral blood picture was due to a hemodilution.

Effect of Estrogen on the Metabolism of Protein-Bound Iodine.—A relationship between gonadal and thyroidal functions has long been suspected and frequently studied, with conflicting or inconclusive results. The present investigation was, therefore, initiated to examine more thoroughly the effect of estrogen on thyroid function and protein-bound iodine. The results indicated that estrogen increased the protein-bound iodine content of the thyroid and its hormonal turnover.

Loss of Appetite for Alcohol and Alcohol Beverages Produced in Rats by Treatment with Thyroid Preparations.—Self-selection experiments have shown that homeostasis of an organism is maintained not only by the physiological regulators but also by behavioral regulators that are manifested in the activities of the total organism. In the common laboratory rat appetite has proved to be such a reliable guide to dietary needs that it can be used as a tool for the study of the nutritive value of food-stuffs and of the factors involved in their utilization as well as an indicator of the specific mechanisms involved in the functioning of the various endocrine glands.

From previous experimental experience the preference for alcohol solution over water indicates that rats regard alcohol as a nutritive substance and not as a poison. The food value of alcohol was demonstrated in the alcohol experiments by the observation that although some rats on the 16% and 24% concentrations derived 40%-50% of their total caloric intake from alcohol over periods of 10-15 months they remained in excellent shape and, in fact, were some of the healthiest looking animals that the authors have had.

Almost immediately after thyroid powder in a 1% concentration was added to the food, the rats stopped drinking the alcohol solution, drank much more water, and ate more food. Feeding thyroid powder had the same effect on the appetite for wine and beer and whiskey. Other thyroid preparations, thyroxine, and triiodothyronine were equally effective.

It might follow, then, that in man treatment with thyroid preparations might help alcoholics through reducing their appetite for alcohol.

The Inhibition of Hypophysectomy-Induced Changes in the Rat Submaxillary Glands.—The present study indicates that, of all the substances evaluated, only the simultaneous administration of testosterone and thyroxine will inhibit the histologic and proteolytic enzyme changes induced in the rat submaxillary gland by hypophysectomy. A correlation was noted between the size of the submaxillary granular tubules and the degree of protease activity. This suggests that these tubules are the source of this enzyme.

Evidence for Diencephalic Regulation of Aldosterone Secretion.—The roles of the thalamus and hypothalamus in endocrine physiology represent a new and important field of research. The cells in the supraoptic and paraventricular nuclei have been shown to form neurosecretory granules, presumably antidiuretic hormone or a precursor, which pass along nerve axons to the neurohypophysis. Lesions in the hypothalamus and median eminence have also been shown to disturb hypophysial gonadotropic, thyrotropic, and adrenocorticotropic functions. It appears from the work reported here that a neurohumoral aldosterone-stimulating center may also be located within this important area of the brain.

Alterations in Chick Thyroid Function Induced by Cobalt.—The goitrogenic action of cobaltous salts in man has recently been reported by these authors. The goiters which followed long-term administration of cobaltous chloride showed colloid depletion, cellular hypertrophy, and hyperplasia and were accompanied by laboratory evidence of suppression of thyroid function and occasionally by clinical myxedema. The goiters disappeared on withdrawal of the drug.

This report describes acute alterations in chick thyroid function induced by cobalt and attempts to elucidate the mechanism of action by comparing its effects to those of TSH and propylthiouracil.

Effect of Phosphate in Enhancing the Action of Triiodothyronine.—During the course of studies in dogs designed to determine the effect of triiodothyronine on the oxygen consumption of kidney tissue, it was observed that the intravenous administration of tri-

iodothyronine to animals receiving a continuous infusion of phosphate produced a marked and rapid increase in oxygen consumption and death from what appeared to be a thyroid storm.

The high mortality noted in these experiments suggests that a similar metabolic synergism might profitably be considered in patients with elevated plasma phosphate due to renal disease who are given T-3 for therapeutic or diagnostic reasons.

The Inhibitory Effect of Reserpine on ACTH Secretion in Response to Stressful Stimuli.—The obligatory participation of the central nervous system, particularly the hypothalamus, in the mechanism through which secretion of the adrenocorticotropin (ACTH) is stimulated has been supported by numerous experiments. Pharmacologic blockade in the central nervous system, as a means of further clarification of this mechanism, offers certain advantages over the placement of electrolytic lesions.

A single injection of reserpine in young male rats resulted in acute hypersecretion of corticotropin, as determined by adrenal ascorbic acid concentration four hours after the injection.

After daily administration of reserpine for five to seven days, the last injection of reserpine, unlike the first one, did not result in corticotropin release.

Chronic administration of reserpine, in daily doses as low as 0.125 mg/100 gm. for seven days, resulted in inhibition of the hypersecretion of corticotropin in response to two stressful stimuli, exposure to ether and injection of histamine.

Neurohypophysis and Water Metabolism in the Toad, Bufo Bufo (L).—The role of the neurohypophysis in the water metabolism of the toad Bufo bufo (L) was investigated by sectioning of the preoptic-hypophysial tract. The neural lobe of the neurohypophysis degenerated after this operation.

The experiments indicate that water-balance principle is liberated from the neurohypophysis during dehydration, but the cutaneous and renal responses to dehydration have so far been found to be independent of neurohypophysial activity in the toad.

Density as an Index of the Effects of Estrogens on Bone.—Estrogenic substances stimulated increases in the densities of femora of treated mice, presumably by causing proliferation of medullary bone.

Effect of Testosterone on Circulating Eosinophils in the Guinea Pig.—Direct evidence for an eosinopenic effect of testosterone in the guinea pig is given in this report.

Thyroid in B-12 Deficient Chick Embryos.—An enlarged thyroid gland was observed in vitamin-B-12-deficient chick embryos during the study of the pathologic changes associated with this deficiency. This study suggests that the thyroid from vitamin-B-12-deficient embryos may be hypofunctional.

The Gonadal Regulation of Cholesteremia in the Rat.—Male rats were found to have lower serum cholesterol levels than females. Castration and/or sex hormone treatment of these rats was shown to influence cholesteremia both before and after the introduction of a hypercholesteremic feeding procedure. It appears that "maleness," represented either by an intact gonadal system or by replacement hormone, favors lower serum cholesterol levels in the rat.

The Influence of Vitamin B_{12} Deficiency on the Uptake of I^{131} by the Thyroid Gland in Adult and Embryonic Chickens.—The thyroid glands found in embryos from vitamin-B_{12}-deficient hens exhibit reduced ability to concentrate I^{131}. Monoiodotyrosine, diiodotyrosine, thyroxine, and iodide are present in the deficient glands, as indicated by paper radiochromatography.

Studies on the Nature of the Thyroid-Pituitary Interrelationship.—It has generally been held that hormone secretion by the thyroid and thyrotropin (TSH) output by the anterior pituitary are homeostatically associated in a "feed-back" type of relationship. It is felt that the data obtained in these experiments are not consistent with the simple classical "feed-back" theory of thyroid-pituitary interrelations. It is likely that the pituitary cells secreting TSH are influenced not only by the actual circulating level of thyroid hormone(s) but by one or more of its peripheral actions.

Changes in Bones and Joints of Underfed Mice Bearing Anterior Hypophyseal Grafts.—In mice and guinea pigs, transplants and extracts of anterior hypophysis promoted skeletal growth and development; they also increased the incidence and advanced the onset of degenerative joint disease, the active principle being the somatotropin fraction.

In male mice of Strain A, restriction of food intake to about two-thirds of the amount consumed ad libitum retarded epithyseal development and decreased the incidence and severity of degenerative joint disease. Transplants of anterior hypophysis obtained from closely related donor animals reversed these changes, accelerating skeletal development and increasing the incidence of degenerative joint disease.

The Effects of Carbutamide (BZ-55) on Blood Sugar Levels of Depancreatized Dogs Given Insulin.—The results clearly indicate that a single dose of BZ-55 injected into normal dogs had rapid hypoglycemic effects, but these effects could not be elicited in pancreatectomized dogs treated with constant infusions of insulin. These data strongly suggest that BZ-55 does not act acutely in normal animals by inhibiting insulin-destroying agents.

The Effect of Furadroxyl Treatment and X-Irradiation on the Hyaluronidase Concentration of Rat Testes.—On the basis of the evidence presented in this paper and in earlier related studies, it is suggested that the spermatid is the testicular cell responsible for the production of hyaluronidase.

News and Comment

GENERAL NEWS

Specialists Certified in Pediatric Allergy by the American Board of Pediatrics, Inc.—The following physicians were certified in pediatric allergy by the American Board of Pediatrics, Inc., in Washington, D. C., March 31, 1957.

Chambers, Van Vleck, Rochester, N. Y.
Crawford, Lloyd Vernon, Memphis.
Lanoff, Gilbert, Chicago.
Lent, Virginia Catherine, Hempstead, N. Y.
Marks, Meyer B., Miami Beach, Fla.
Nelson, Thomas Lothian, Eldridge, Calif.

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., in Washington, D. C., April 5, 6, and 7, 1957.

Abrahamsen, Edwin Howard, Stroudsburg, Pa.
Baird, Robert L. S., Washington, D. C.
Bartfeld, Rela, New York.
Baughman, Howard Elsworth, Jr., Portsmouth, Ohio.
Berman, Bernard A., Boston.
Bradford, Mary E., Northport, N. Y.
Bramley, Gertrude Leland, Baltimore.
Bugg, Charles Paulett, Raleigh, N. C.
Cassara, Sam, Rochester, N. Y.
Dixon, Morris S., Jr., Wooster, Ohio.
Donner, Leon, Baltimore.
Eisenberg, Melvin, Queens, N. Y.
Ellis, William C., Red Bank, N. J.
Esterly, Katherine Louise, Wilmington, Del.
Fenzl, Robert C., Lockport, N. Y.
Font, Wallace, Rochester, N. Y.
Ford, Douglas, Jr., East Orange, N. J.
Fried, Sylvia Kosovsky, Englewood, N. J.
Geyer, George E., Walpole, Mass.
Giesel, Louis Oscar, Louisville, Ky.
Goldman, Herbert I., Bayside, L. I., N. Y.
Gordon, Benjamin D., Stratford, Conn.
Griese, George Gregory, Jenkintown, Pa.
Haggerty, Virginia Irene, Mamaroneck, N. Y.
Halpin, Mary Aiden, South Braintree, Mass.
Holliday, Malcolm Alexander, Pittsburgh.
Kercher, Ervin F., Kalamazoo, Mich.
Koreen, Joseph Moses, Ottawa, Ont., Canada.
Kushnick, Theodore, Linden, N. J.
Liang, Milly Chu-Hsing, Chicago.
Lindemann, Lillian Chambers, Richmond, Va.
Ling, Julia Kuo-fang, Yonkers, N. Y.
Lord, Robert Mendon, Jr., Providence, R. I.
McCloskey, Rosemary Gilmore, Bloomfield, N. J.
Mantell, Harriet Baylies, Newark, Del.
Marcus, Edwin L., Ann Arbor, Mich.
Melia, Daniel John, Yonkers, N. Y.
Mertz, Joanne E., Petoskey, Mich.
Mogil, George David, Lancaster, Ohio.
Motamedy, Farokh Frank, Augusta, Ga.
Orleans, Julian, Livingston, N. J.
Painter, John William, Fredericksburg, Va.
Parker, William S., Baltimore.
Peirce, Frederick Arthur, Jr., Edgewood, R. I.
Perlman, Abraham, Philadelphia.
Rashkind, William J., Bala-Cynwyd, Pa.
Rawson, Helen Huber, Lansdale, Pa.
Rheney, John Watson, Orangeburg, S. C.
Ripberger, Frank M., Jr., Alexandria, Va.
Schessel, Jesse, Tuckahoe, N. Y.
Sherwood, Edward Silliman, New Brunswick, N. J.
Simpson, Dazelle Dean, Miami, Fla.
Smelzer, Marilyn F., Rochester, N. Y.
Smull, Ned Willits, Kansas City, Mo.
Stambler, Alvin A., Baltimore.
Stubbs, Samuel S., Warren, Ohio.
Trevathan, G. Earl, Greenville, N. C.
Walker, James, Glastonbury, Conn.
Walton, Richmond Lee, Stratford, Conn.
Waters, Richard Jerome, Bethany, Conn.
Whitten, Charles Francis, Detroit.
Wiswall, William Cobb, Lynnfield Center, Mass.

Special Foreign Certificate: Adiao, Amparo C., Brooklyn.

The following listed physician was certified at New Orleans on Feb. 22, 1957, and will receive a regular certificate (he was not eligible to receive this certificate until April 1, 1957): Alison, James Fairly, Jr., Selma, Ala.

Registry of Pediatric Pathology.—Under the auspices of the American Academy of Pediatrics, a special registry, devoted to Pediatric Pathology, is to be established as one of the components of the American Registry of Pathology of the Armed Forces Institute of Pathology. The success of other component registries in collecting adequate source material for the study of rare and unusual disease processes in several branches of medicine has prompted the Armed Forces Institute of Pathology to devote a special section to the pathology of diseases of children. The advantages of this procedure are many. Making available the extensive facilities of the Armed Forces Institute can add greatly to the thoroughness with which specimens can be processed. Collection of large numbers of specimens yields statistical data not obtainable otherwise. Accessibility, for the profession at large, to data and material from diverse sources facilitates the study of topics of special interest, especially for persons with special techniques.

The advantages of a special Registry of Pediatric Pathology accrue from the special character of pathology as seen in children, where growth processes must always be considered along with disease and where disturbances of growth render this field of pathology distinctive from other fields. The Registry of Pediatric Pathology will limit its material only with respect to the age group involved. Adequate cataloguing, maintenance of records, and availability of material are primary objectives in the procedure. In addition, a consultation service will be provided for all pathologists, similar to that offered by the other component registries. Leading authorities in pediatric pathology in this country and abroad will thus be on call for questions in their special fields of interest. The material will also be made available for teaching purposes, and it is hoped that, in the future, the Registry may provide a position for training in pediatric pathology. The support of all pathologists and pediatricians, therefore, is needed to insure the success of this new division. All inquiries concerning it should be addressed to the Registry of Pathology at the Armed Forces Institute of Pathology. Any interested physician is invited to visit the Registry at his convenience at Walter Reed Medical Center, 6825 16th St., N. W., Washington 25, D. C.

The Committee on Pediatric Pathology of the American Academy of Pediatrics consists of Drs. Sidney Farber, Boston, Chairman; Edith Potter, Chicago; Irving Wolman, Philadelphia; William B. Kiesewetter, Pittsburgh; George H. Fetterman, Pittsburgh; Robert S. Cleland, Los Angeles; Major Daniel Stowens (MC), of the Armed Forces Institute of Pathology, is Secretary of the Committee.

Booklets for Children.—Two very interesting booklets for children about to enter a hospital have been prepared at Memorial Center, New York. The booklets, "Inside the Hospital" and "All About an Operation," by Helen B. Radler, explain to children in very simple language the need for hospitalization and operations and the procedures involved.

"Inside the Hospital" likens a child's body to an automobile and draws an analogy between the breakdowns and repairs of cars and the human body. Hospital procedures are explained, as well as the functions of doctors and nurses. "All About an Operation" outlines briefly the procedures involved in an operation and hospital care and the reasons for surgery. Both are charmingly and amusingly illustrated by Ginnie Hofmann.

The booklets are available for 25 cents each from the Memorial Center, 444 E. 68th St., New York 21. Proceeds are donated to the Children's Division of the Society of Memorial Center.

ANNOUNCEMENTS

Residency in Pediatric Oncology.—Applications for the residency from Jan. 1, 1958, to Dec. 31, 1958, in pediatric oncology at Memorial Center for Cancer and Allied Diseases in New York will be received up to Aug. 1, 1957. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary is $3600 annually plus maintainance. For application forms and information write to Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York 21.

Fellowship in Newborn Research.—A Fellowship in Newborn Research is available in the Department of Pediatrics of the University of Pittsburgh School of Medicine, beginning July 1, 1957. A balanced program of research, clinical training, and teaching is offered. Completion of two years of approved pediatric residency is required for eligibility. The stipend is $4000 per year.

For further information, write Dr. E. R. McCluskey, 125 DeSoto St., Pittsburgh 13.

GENERAL NEWS

Home Nursing and First Aid Guide.—A new "common sense" kind of home nursing and first aid guide for family use, stressing prevention of accidents and illness, has been published by the Medical Department of the Equitable Life Assurance Society. The 256-page illustrated pocket-size volume, entitled "Home Health Emergencies," developed from an original manuscript by Granville W. Larimore, M.D., is available on individual request without charge or obligation from the Equitable's Bureau of Public Health, 393 7th Ave., New York 1.

The Medical Department has also issued a leaflet based on the book which gives basic first-aid rules in brief. The leaflet has space for notation of the phone number of the family physician, ambulance service, hospital, police station, and fire department. It also has a coupon for use in requesting a family copy of "Home Health Emergencies." The leaflet, titled "First Aid: If You Had to Act Now, Would You Know What to Do?", is available in bulk for distribution by private practitioners, medical institutions, health organizations, and agencies.

Discontinuation of Medical Book Shipments to Korea.—The American-Korean Foundation and the United States Army Medical Service have announced the discontinuation of their joint project of shipping medical books contributed by individual physicians, medical schools, hospitals, and state and local medical societies to Korea.

Books should not be sent to the Sharpe General Depot in California as in the past, for facilities no longer exist for packing and transshipping to Korea.

In making the announcement, Howard A. Rusk, M.D., President, American-Korean Foundation said, "The response of physicians and medical groups throughout the country for our appeal for books for Korean medical schools has been so generous that further contributions are not needed."

Books

BOOKS RECEIVED

Rheumatic Diseases, Rheumatism and Arthritis. By Heinrich G. Brugsch. Price, $10.00. Pp. 330, with 58 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1957.

Expectant Motherhood. By Nicholson J. Eastman. Third edition, revised. Price, $1.75. Pp. 198, with 13 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

Official A. M. A. Book of Health. Edited by W. W. Bauer. Price, 35 cents. Pp. 320. Dell Books, 200 Fifth Ave., New York 10, 1956.

Administration of Maternal and Child Health Services: Second Report. By Expert Committee on Maternal and Child Health. WHO Technical Report Series No. 115. Price, 30 cents. Pp. 28. World Health Organization, Palais des nations, Geneva, 1957.

Changes in Body Water Compartments During Growth. By Bent Friis-Hansen. Price, Cr. 25.00 (Danish). Pp. 68, with 20 tables. Ejnar Munksgaards Forlag, Nørregade 6, Copenhagen, 1956.

Tuberculose initiale. By Franck Tissot. Price, 1500 fr. Pp. 184, with 32 illustrations. Gaston Doin & Cie, 8, place de l'Odéon, Paris, 6e, 1956.

Six Children. By Estelle J. Foote. Price, $5.50. Pp. 317. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

The Merck Manual. Edited by Charles E. Lyght. Ninth edition. Price, $6.75. Pp. 1888. Merck & Co., Inc., Rahway, N. J., 1956.

Retarded Children Can Be Helped. By Cornell Capa and Maya Pines. Price, $5.00. Pp. 159, with about 80 illustrations. Channel Press, Great Neck, N. Y., 1957.

The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki. By J. V. Neel and W. J. Schull. Price, not given. Pp. 241, with 15 illustrations. National Academy of Sciences-National Research Council, Washington 25, D. C., 1956.

Dode Has Her Tonsils Out. By Henri Grady Skoie, Adelia De Vore, and Evelyn Koperski. Price, $2.50. Pp. 30, with 9 illustrations. Pageant Press, Inc., 130 W. 42d St., New York 36, 1956.

Directory for Exceptional Children. Second edition. Edited by E. Nelson Hayes. Price, $4.00 cloth, $3.00 paper. Pp. 256. Porter Sargent, 11 Beacon St., Boston 8, 1956.

Pediatric Dentistry. By M. Michael Cohen. Price, $14.75. Pp. 607, with 395 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1957.

Handbook on Poliomyelitis. By Joseph Trueta, A. B. Kinnier Wilson, and Margaret Agerholm. Price, $3.75. Pp. 139, with 26 illustrations. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, 1957.

Ultramicro Methods for Clinical Laboratories. By Edwin M. Knights, Roderick P. MacDonald, and Jaan Ploompuu. Price, $4.75. Pp. 128, with 18 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1957.

Proceedings of the Third National Cancer Conference. Sponsored by American Cancer Society, Inc., and National Cancer Institute, U. S. Public Health Service. Price, $9.00. Pp. 961, with numerous illustrations. J. P. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1957.

BOOK REVIEWS

Pre and Postoperative Care in the Pediatric Surgical Patient. By William B. Kiesewetter, M.D. Price, $7.00. Pp. 347, with 49 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago, 1956.

This volume is designed not as a text but as a concise outline of pre- and postoperative care in the field of pediatric surgery. The author points out that it is written with the "occasional pediatric surgeon" in mind.

The early sections of the book deal with the general preoperative considerations and with general postoperative considerations. There is a short but beautifully written chapter dealing with the child's emotions in surgery. There also are chapters of outline type regarding fluid and electrolyte balance and anesthesia, with a minimum of discussion. The postoperative considerations are concerned with the normal postoperative period and the abnormal postoperative period. The chapter concerned with care of the wound is presented very succinctly.

The final section is entitled "Specific Pre and Postoperative Considerations." These are presented as conditions necessitating operation grouped according to the various body regions. In outline form, under each condition, are listed (1) required studies, (2) elective studies, (3) differential considerations, (4) preoperative treatment and orders, and (5) postoperative management. Finally, the appendices illustrate forms used in pre- and postoperative care, show computations for treatment of dehydration and acidosis, list various drug doses, and state normal laboratory studies.

This would seem to be an excellent handbook for the medical student, house officer, and practicing surgeon, if it can be used in the manner for which it is designed. Its concise outline form should stimulate one to further reading, and this is facilitated by excellent bibliographies at the end of each chapter. It is believed that this volume will fill a definite need in this particular area of surgery.

Radiology of the Alimentary Tract in Infancy. By Roy Astley, M.B., M.R.C.S., D.M.R. Price, not given. Pp. 287, with numerous illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1956.

The addition of a new book to the already too voluminous medical literature is seldom met with open arms unless the author has found and filled a definite void. Roy Astley has performed such a feat in writing a concise book of 287 pages on the "Radiology of the Alimentary Tract in Infancy."

This book is well bound and is characterized throughout by easy readability. The x-ray reproductions are of satisfactory quality, being printed as negatives, and demonstrate the pathology in each case. An indication of the care used in the preparation of this book is the matching of the x-rays to the page on which their pathology is discussed.

The over-all format is that to which the alimentary tract lends itself so well. The author paralleled the proximal and distal portions of the alimentary tract with the proximal and distal chapters of the book. This method of presentation allows various conditions to be easily located without reference to the index. The index is also adequate, and so no reluctance in referring to it is encountered.

The subjects are broken down into various subgroups, which include a general introduction, pathological classifications, radiological findings, and varying clinical features. An interesting adjunct, and one of value to a beginning radiologist, is the concentration of barium for certain procedures. Each subject is followed by pertinent case histories. These histories are presented in different type than the remainder of the book, so that they can be omitted if this is desired. In general, the histories add little to the discussion in the general text.

The author does not include any discussion on "normal findings." In his preface he states that "this useful knowledge . . . springs only from practice." However, comments by a man of such wide experience would have been of invaluable aid in interpreting the near-pathological findings that are so particularly found in pediatric radiology.

In general, this book is of inestimable value as an introduction to radiology of the infant's alimentary tract. The general appearance, excellent presentation, and general format lend it readily to satisfying reading. The particular need that it fills would be to the beginning radiological trainee and to the pediatrician who wishes a rapid reference to the possibilities of exploration of the gastrointestinal tract in infancy.

Ciba Foundation Symposium on Paper Electrophoresis. Edited by G. E. W. Wolstenholme and Elaine C. P. Miller. Price, $6.75. Pp. 232, with 74 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

By combining formal presentations on various facets of the subject of paper electrophoresis with informal and sometimes lengthy discussion, 22 of the world's pioneers in this field have provided the reader with a rather comprehensive review of this popular laboratory procedure. Detailed descriptions are given of the types of basic apparatus which have been employed and of the conditions under which electrophoretic separations are carried out. Emphasis is placed upon the importance of interpreting results of serum protein analysis with proper consideration to such variables as drying of the paper strips, type of protein stain employed, time of staining and rinsing, and method of analyzing the completed and stained electrophoretic record. Considerable attention is given the method of analyzing stained records by photometric scanning, and the many possible sources of error are adequately pointed out. A description is given of the methods of studying nonprotein substances or protein-nonprotein complexes such as lipids, carbohydrates, and hemoglobins, including instructions for staining and analyzing these compounds. References are given to the electrophoretic study of substances of small molecular weight, such as amino acids, nucleic acids, nucleotides, and other degradation products of complex compounds. A more detailed index would be helpful to the reader interested in obtaining information on specific subjects.

The Psychoanalytic Study of the Child: Vol. 11. By Ruth S. Eissler and others. Price, $8.50. Pp. 470. International Universities Press, Inc., 227 W. 13th St., New York 11, 1956.

The eleventh volume of this annual publication on the psychoanalytic approach to problems of childhood is divided into theoretical contributions, normal and pathological development, clinical contributions, and applied psychoanalysis.

For those interested in the psychodynamics of behavior this book is of great value, provided the reader is well-familiar with psychoanalytic terms. For the pediatrician without this background the discussions will be too involved in their very detailed approach to theoretical questions.

The reader who wishes to study psychoanalytic concepts will find "Notes on the Reality Principle" very helpful in learning to understand such terms as pleasure principle, reality principle, ego structure, etc. The paper on "Unusual Variations in Drive Endowment" will be of great interest to students of human development, but, as it is based on the analysis of only three cases, the material could not be readily used for generalization and thus for diagnostic or therapeutic purposes of the pediatrician. The same may be said for the two last articles in this chapter, "On the Development of Maternal Feelings in Early Childhood: Observations and Reflections," and "Some Evidence of Deviational Development in Infancy and Childhood."

The intricacies of psychotherapy are well demonstrated in "Observations on the Psychotherapy of Borderline and Psychotic Children," and the article on "The School's Role in Promoting Sublimation" is good reading for any pediatrician, educator, or other person concerned with the bringing up of children.

Die Pflege des gesunden und des kranken Kindes. By W. Catel. Price, $10.00. Pp. 665, with 336 illustrations. Georg. Thieme Verlag, Herdweg 63, (14a) Stuttgart N American zone), 1956.

This is the fifth edition of a textbook on nursing care, primarily directed to nursing students. The book covers basic and anatomical facts and very detailed instruction in the care of the well and the sick child. Hospital nursing is discussed with detailed instructions in every area of nursing activity. One is struck at once by the great preoccupation with the physical management and the relative dearth of any information as regards the child's normal growth and development, considerations of variations within the normal, consideration of emotional growth, consideration of the effects of illness on the child's subsequent development, and other aspects of child care which are now considered important by most American pediatricians and American schools of nursing. There is a wealth of basic and well-presented information of use to nursing students. But there is a regretable rigidity in the approach to a child which is thoroughly unphysiological and appears dated to this reviewer. For example, nursing is regularly performed at four-hour intervals, starting at 6:00 a. m. and finishing at 10:00 p. m. The eight-hour fast is initiated beginning with the child's second day of life! Many of the procedures reflect therapeutic thinking of years past and of dubious value. These include the various therapeutic baths and packs, many of which are in conflict with modern concepts of

physiology. Detailed instructions for the nursing management and observation of specific diseases reveal similar inaccuracies. For example, the specific recommendation to place children with pneumonia into the open air, even in the winter during snowfall.

It is most instructive for us to review the sources of many fads still to be found in American pediatric practice, and it is regretable that a modern textbook containing much excellent teaching material would perpetuate many such unphysiological measures in the nursing care of sick children.

The book appears to fill a specific need in the field of German nursing education, but it would appear to have no great value to practitioners in this country.

Die Eigenart der Kindlichen Hirntätigkeit: Vol. 2. By Albrecht Peiper. Price, DM 44.50. Pp. 588, with 172 illustrations. VEB Georg Thieme, Hainstr. 17/19 Aufg. C, Leipzig C. 1, 1956.

The second edition of Peiper's monumental work is a veritable mine of information for pediatricians and neurologists, and it represents German scholarship and scientific thoroughness at their best. For years Peiper and his associates have been making and documenting detailed observations of the motor behavior of infants and their responses to all manner of stimuli from birth on.

The detailed descriptions of the developmental patterns as regards sensory development, position and movement, the neurologic factors of respiration, nutrition, sleep, as well as a complete discussion of normal and abnormal reflexes, are discussed from the point of view of development and maturation. Each chapter ends with a lucid summary and a rather complete bibliography of the world literature.

Nothing like this discussion of developmental neurology exists in the American literature, and it is to be hoped that early translation into the English language will be possible for this unique and thorough work, which is well illustrated.

Säuglings-Enteritis. By A. Adam, O. H. Braun, H. Hungerland, G. Ilgner, F. Kauffmann, H. W. Ocklitz, F. Orskov, E. F. Schmidt, D. Schreier, and R. Thurau. Price, $14.30. Pp. 534, with 43 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N (American zone), 1956.

This book represents a first-rate effort on the part of the authors to provide an up-to-date treatise of the status of diarrhea of the newborn. The book contains excellent data on the bacteriology of pathogenic Escherichia coli and data on the epidemiology of diarrhea of the newborn caused by a number of known pathogens. This monograph also discusses the pathologic picture and fluid and electrolyte problems, as well as therapy of diarrhea of this condition. Suggestions for prophylaxis conclude this volume.

It is hoped that this volume will receive an early translation into the English language. It represents authoritative and detailed up-to-date information and is an excellent source of recent world references for the entire field.

Ciba Foundation Symposium on Ageing in Transient Tissues. Edited by G. E. W. Wolstenholme and Elaine C. P. Millar. Price, $6.75. Pp. 263, with 96 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

This symposium, the second of an annual series on aging, was held July 5-7, 1955, under the auspices of the Ciba Foundation of London. The aging of transient tissues, that is, those tissues having a shorter normal life than that of the organism as a whole, is considered from a variety of aspects. Although much of the material presented is of theoretical interest, that concerning metabolic changes in the placenta with aging, the effects of growth hormone (somatotropic hormone) in the causation of fetal gigantism, and the changes produced in the offspring of rats whose mothers are treated with cortisone during gestation may have direct clinical implications in pediatrics. On the whole, however, the book is of major interest as it pertains to aging in the placenta, the reproductive organs, and the red blood cell.

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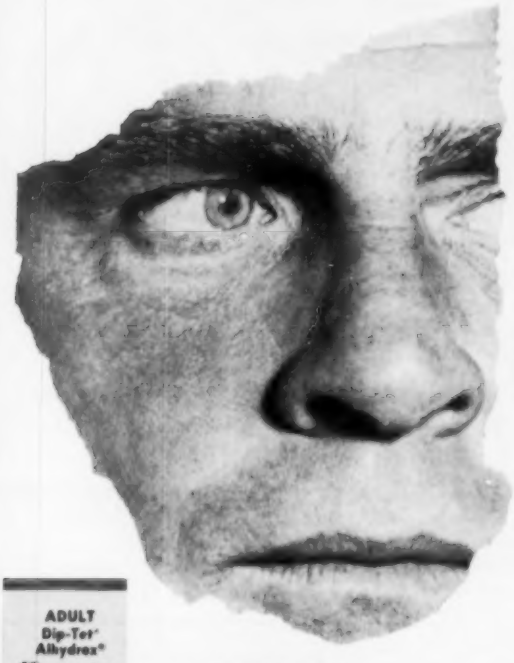

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[1]Edsall, Geoffrey: *Am. Jour. Public Health 42:393-400, 1952.*
[2]Long, E. P. and Sartwell, P. E.: *Bull. U.S. Army M. Dept. 7:371-385, 1947.*
[3]Editorial, *New England Jour. of Med. 237:411-413, 1947.*
[4]Edsall, Geoffrey; Altman, James S.; and Gaspar, Andrew J.: *Am. Jour. Public Health 44:1537-1545, 1954.*

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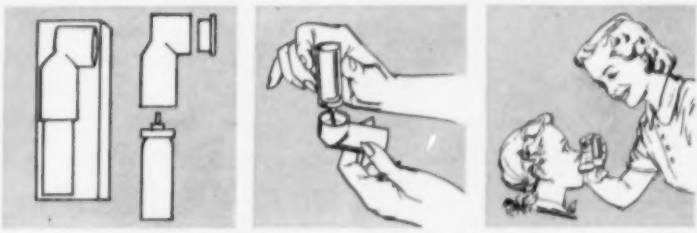

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(1) Smith, N. J., and Rosello, S.: J. Clin. Nutrition *1*:275, 1953.
(2) Coleman, D. H.; Stevens, A. R., Jr., and Finch, C. A.: Blood *10*:567, 1955.

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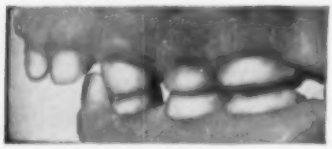

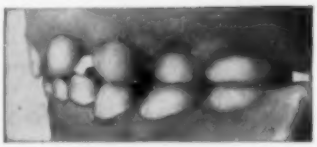

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1. Jackson, P. L.: Iron Deficiency Anemia in Infants, Editorial, J.A.M.A. *160*:976 (Mar. 17) 1956.

2. Martin, E. A.: Roberts' Nutrition Work with Children, Chicago, The University of Chicago Press, 1954, p. 211.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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1. Kent-Jones, D.W.: Modern Cereal Chemistry, ed. 3, The Northern Publishing Co., Liverpool (1939).

2. Heupke, W., and Kolb, A.: Mechanism of the Beneficial Action of Alimentation of Oats in Diabetes, Deutsche Ztschr. Verdauungeskr. *13*:111 (1953).

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32 calories per fl. oz.

SUGGESTED 24-HOUR FEEDINGS FOR FULL-TERM INFANTS

AGE	OUNCES VARAMEL	OUNCES WATER	(USE ONLY ONE) TBLS. DEX.-MALT.	TBLS. CORN SYRUP	APPROX. CALS. PER OZ.
Newborn	10	14	1	½	14
2nd Week	13	15	2	1	17
3rd Week	13	13	3	1½	19
1 Month	13	13	4	2	20

Made entirely from Grade A Milk (U. S. Public Health Service Milk Code) modified by replacement of the milk fat with animal and vegetable fats and by the addition of vitamins and iron. No carbohydrate has been added.

Maximum Flexibility

Low in Cost

Simple to Use:

+ CARBOHYDRATE + WATER

Approximate Analysis

Protein	4.9%	Calcium	0.19
Carbohydrate	8.3	Phosphorus	0.15
Fat	5.8	Iron	0.0016
Ash	1.2	Moisture	79.8

Calories per fl. oz., 32

Varamel

THE BAKER LABORATORIES, INC.

Milk Products Exclusively for the Medical Profession

MAIN OFFICE: CLEVELAND 3, OHIO

PLANT: EAST TROY, WISCONSIN

The "Snifflers"

they always have

red noses and the sniffles

hay fever runs in their family

When they bring their sore noses and congested heads to you for relief – there's a whole family of reliable vasoconstrictor-decongestive Neo-Synephrine products ready to give them quick and lasting comfort.

The NEO-SYNEPHRINE® *hydrochloride*

"hay fever comfort" family:

- **Prompt and Prolonged Decongestion**
- **Sinus Drainage and Aeration**
- **In practically all cases**

NO IRRITATION
NO SEDATION
NO EXCITATION

Nasal Solutions 0.25%, 0.5% and 1%

Adult Nasal Spray 0.5%
Pediatric Nasal Spray 0.25%

plastic, unbreakable squeeze bottles, leakproof, deliver a fine mist.

with Zephiran® chloride 1:5000, antibacterial wetting agent and preservative for greater efficiency

Winthrop LABORATORIES
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Neo-Synephrine (brand of phenylephrine) and Zephiran (brand of benzalkonium, as chloride, refined), trademarks reg. U. S. Pat. Off.